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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

September 20, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

HOBART W. HARRIS, M.D.	Panel Chair
MURAD ALAM, M.D.	Panel Member
KELLY HUNT, M.D., FACS	Panel Member
KAREN BURKE, M.D., Ph.D.	Panel Member
MICHAEL MILLER, M.D., FACS	Panel Member
GREG CAMPBELL, Ph.D.	Panel Member
JAMES HOLMES IV, M.D., FACS	Panel Member
STEVEN WOLF, M.D.	Panel Member
FLURYANNE LEACH, M.S., RN	Panel Member
L. BARTH RELLER, M.D., FACP	Panel Member
WILLIAM HICKERSON, M.D., FACS	Panel Member
JEAN PATEL, Ph.D., D(ABMM)	Panel Member
GEETIKA SOOD, M.D.	Panel Member
SUSAN ELMORE, M.S., D.V.M., DACVP, DABT, FIATP	Panel Member
MICHELLE LOTT, RAC	Industry Representative
JO-ELLEN DE LUCA	Patient Representative
YUSEF SAYEED, M.D., M.P.H., M.Eng., CPH, CMRO, CME, COHC, EIT	Consumer Representative
EVELLA F. WASHINGTON	Designated Federal Officer

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Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

ROBERT M. CALIFF, M.D., MACC
Commissioner of Food & Drugs

BINITA ASHAR, M.D.
Director, Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health

ANGELA KRUEGER
Associate Director for Regulations and Guidance
Office of Device Evaluation
Center for Devices and Radiological Health

PETER KIM, M.D.
Medical Officer
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

FALLON SMITH
Press Contact

FDA PRESENTERS:

MELISSA BURNS
Senior Program Manager
Office of Combination Products

CHARLES DURFOR, Ph.D.
Scientific Reviewer
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health

CYNTHIA J. CHANG, Ph.D.
Biomedical Engineer
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health

BRANDON KITCHEL
Microbiologist
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health

LAURA MARQUART, M.D.
Medical Officer
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health

KAREN NAST, M.S., RN
Nurse Consultant/MDR Analyst
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Devices and Radiological Health

GUEST PRESENTER:

FINN GOTTRUP, M.D., D.M.Sci.
Professor of Surgery
University of South Denmark

OPEN PUBLIC HEARING SPEAKERS:

ERIC J. LULLOVE, D.P.M., CWS, FACCWS
Medical Director, West Boca Center for Wound Healing
Association for Advancement of Wound Care

DENIS WATSON
Managing Director, Manukamed

JOAN M. SIEGEL
President, CEO, Puremedy, Inc.

MARCIA NUSGART, RPh
Executive Director, Alliance of Wound Care Stakeholders

GREGORY SCHULTZ, Ph.D.
Research Foundation Professor
Director, Institute for Wound Research
University of Florida

DOROTHY WEIR, RN, CWON, CWS
Certified Wound Nurse
Osceola Regional Medical Center
Health Central Hospital

RANDALL WOLCOTT, M.D.
Director, Southwest Regional Wound Care Center

JUDITH O'GRADY, M.S.N., RN
Corporate Vice President Global Regulatory Affairs
Integra LifeSciences Corporation

MARISSA J. CARTER, Ph.D., M.A., MAPWCA
President, Strategic Solutions, Inc.

CAROLINE FIFE, M.D.
Professor of Geriatrics, Baylor College of Medicine
Executive Director, the U.S. Wound Registry
Co-Chair, Alliance of Wound Care Stakeholders

SUSAN ALPERT, Ph.D., M.D.
Principal, SFA Consulting, LLC
Former Director ODE, CDRH, FDA

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M E E T I N G

(8:01 a.m.)

DR. HARRIS: Good morning. Can you hear me out there? It's 8:00, or 8:01, so I'd like to call this meeting of the General and Plastic Surgery Devices Panel and the Medical Devices Advisory Committee to order. Please be seated.

My name is Dr. Hobart Harris. I am a Professor at the School of Medicine at University of California in San Francisco in the Department of Surgery. I'm also the Chief of General Surgery there, and my area of particular interest or one of my areas of interest has been in wound care and the diagnosis and management of serious soft tissue infections.

I note for the record that the Panel members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding the classification of certain pre-amendment wound care products containing antimicrobials and other drugs that are regulated under product code FRO, Dressing, Wound, Drug. FDA is seeking Committee input on the indications for use, risks to health, and safety and effectiveness of these wound care products and how they should be classified.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And we can start at this end and then work our way around. Please turn on your mic so that everyone can hear you, including our transcriptionist.

MS. LOTT: My name is Michelle Lott, with Lean RAQA Systems. I'm the Industry Representative. My specialty is regulatory and quality systems.

DR. SAYEED: Dr. Yusef Sayeed. I'm the Consumer Representative. I went to medical

school at the University of Kentucky, a sports medicine research fellowship at the Mayo Clinic, my internship at the University of Pennsylvania, residency at West Virginia University in occupational medicine, which is my primary specialty. I'm currently doing an interventional pain fellowship at the Deuk Spine Institute in Melbourne, Florida. And I, as I said, I'm the Consumer Representative.

MS. DE LUCA: Jo-Ellen De Luca, Spartanburg, South Carolina. I am the Patient Representative.

DR. CAMPBELL: I'm Greg Campbell. I'm a biostatistician by training, and I'm an independent consultant at GCStat Consulting.

DR. HOLMES: Jimmy Holmes. I'm an Associate Professor of Surgery at Wake Forest University School of Medicine, and the Director of the Burn Center at Wake Forest Baptist Medical Center in Winston-Salem, North Carolina.

DR. ELMORE: I'm Susan Elmore, and I'm a veterinarian toxicologic pathologist at the National Toxicology Program and the National Institute of Environmental Health Sciences.

DR. HICKERSON: I'm Bill Hickerson. I'm a Professor of Plastic Surgery at the University of Tennessee in Memphis. I run the burn center there at the Firefighters Regional Burn Center and also the wound care center.

DR. ALAM: I'm Murad Alam. I'm a Professor of Dermatology at Northwestern University.

MS. WASHINGTON: My name is Evella Washington. I'm the DFO.

DR. HUNT: I'm Kelly Hunt, Professor of Surgery at the MD Anderson Cancer Center in Houston, Texas, and I'm the Chair of the Department of Breast Surgical Oncology.

DR. MILLER: Mike Miller, I'm the Chair of Plastic Surgery at Ohio State University.

MS. LEACH: Fluryanne Leach. My specialty is infection prevention and control, recently retired from Walter Reed National Military Medical Center.

DR. RELLER: Barth Reller, infectious diseases, medical microbiology, Professor of Medicine and Pathology at Duke University.

DR. PATEL: I'm Jean Patel, from the Antimicrobial Resistance Unit in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention. And my expertise is in the laboratory detection of antimicrobial resistance, surveillance and epidemiology.

DR. SOOD: I'm Geetika Sood. I'm an Assistant Professor at Johns Hopkins University and the hospital epidemiologist at Johns Hopkins Bayview and an infectious disease physician.

DR. WOLF: I'm Steve Wolf. I'm a professor in the Department of Surgery, Vice Chair for Research and Burn Section Chief at Parkland Hospital in Dallas. I'm also the editor for *Burns*, and so I see a lot of stuff that you all don't see that never makes the light of day.

DR. ASHAR: Good morning. My name is Binita Ashar. I'm a general surgeon, and I'm the Director of the Division of Surgical Devices here at the Center for Devices and Radiological Health at the U.S. FDA.

DR. CALIFF: Good morning. Rob Califf, Commissioner of FDA.

DR. HARRIS: Thank you. Members of the audience, if you have not already done so, please sign the attendance sheets that are on the tables by the doors outside.

And now Ms. Evella Washington, who is the Designated Federal Officer for the General and Plastic Surgery Devices Panel, will now make some introductory remarks.

MS. WASHINGTON: Thank you. The Food and Drug Administration (FDA) is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees

from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the classification of certain wound care products containing antimicrobials and other drugs as part of the routine process for device classification. These products are regulated under product code FRO, Dressing, Wound, Drug, and are considered pre-amendments because they were in commercial distribution prior to May 28th, 1976, when the Medical Devices Amendments were enacted, and have not yet been classified under Section 513 of the Federal Food, Drug, and Cosmetic Act.

As part of the classification process, FDA is seeking Panel input on the indications for use, risks to health, and safety and effectiveness of these wound care products, and how

they should be classified. They may be classified in Class I (general controls), Class II (special and general controls), or Class III (premarket approval, requiring demonstration of safety and effectiveness for each product).

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Michelle Lott is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Lean RAQA Systems, LLC.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda or for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the Panel of any financial relationships they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. Thank you.

For the duration of the General and Plastic Surgery Devices Panel meeting on September the 20th, 2016, Dr. Susan Elmore has been appointed to serve as a temporary non-voting member, and Ms. Jo-Ellen De Luca has been appointed to serve as a temporary non-voting Patient Representative.

For the record, Ms. De Luca serves as consultant to the Gastrointestinal Drugs Advisory Committee at the Center for Drug Evaluation and Research, and Dr. Elmore serves as a consultant to the Psychopharmacologic Drugs Advisory Committee at CDER.

These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at

this meeting. These appointments were authorized by Dr. Janice Soreth, Acting Associate Commissioner for Special Medical Programs, on September the 19th, 2016.

Before I turn the meeting back over to Dr. Harris, I would like to make a few general announcements.

Transcripts for today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos for today's meeting can be found on the table outside of the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today's meeting is Fallon Smith.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded. Sorry.

If you would like to present during today's Open Public Hearing session, please register with AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Harris.

DR. HARRIS: Thank you. Before we continue, I'd like to just introduce another member of our panel.

DR. BURKE: I'm Dr. Karen Burke, from New York, from Mount Sinai Medical Center, and I'm a dermatologist and research scientist.

DR. HARRIS: At this point, I'd like to introduce Dr. Robert Califf, who is the Food and

Drug Administration's Commissioner of Food and Drugs. As the top official of the FDA, Dr. Califf is committed to strengthening programs and policies that enable the Agency to carry out its mission to protect and promote the public health.

Previously, Dr. Califf served as the FDA's Deputy Commissioner for Medical Products and Tobacco, from February 2015 until his appointment as Commissioner in February 2016. In that capacity, he provided executive leadership to the Center for the Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiologic Health, and the Center for Tobacco Products.

He also oversaw the Office of Special Medical Programs and provided direction for crosscutting clinical, scientific, and regulatory initiatives, including precision medicine, combination products, orphan drugs, pediatric therapeutics, and the advisory committee system.

Prior to joining the FDA, Dr. Califf was a Professor of Medicine and Vice Chancellor for Clinical and Translational Research at Duke University. He also served as Director of the Duke Translational Medicine Institute and Founding Director of the Duke Clinical Research Institute. A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr. Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with more than 1,200 publications in the peer-reviewed literature.

Dr. Califf has served on the Institute of Medicine committees that recommended Medicare coverage of clinical trials and the removal of ephedra from the market, as well as the Institute of Medicine Committee on Identifying and Preventing Medical Errors and the Institute of Medicine Health Sciences Policy Board. He has served as a member of the FDA Cardio-Renal Advisory Panel and the FDA Science Board Subcommittee on Science and Technology.

Dr. Califf has also served on the Board of Scientific Counselors for the National Institutes of Health and the National Library of Medicine, as well as on the advisory committees for the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Environmental Health Sciences, and the Council of the National Institute on Aging.

While at Duke, Dr. Califf led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative, a public-private partnership co-founded by the FDA and Duke. He also served as a principal investigator for Duke's Clinical and Translational Science Award and the NIH Health Care Systems Research Collaboratory Coordinating Center.

Dr. Califf is a graduate of Duke University School of Medicine. He completed a residency in internal medicine at the University of California, San Francisco and a fellowship in cardiology at Duke.

Dr. Califf, the podium is now yours.

DR. CALIFF: Thanks so much. I'm really excited to be here, and I showed it by spilling my big latte all over my FDA colleague here to the right, but I think we'll recover from that episode. And this will probably be the first time my comments have been shorter than the introduction, but I do appreciate the nice introduction.

This meeting -- I'm really excited to be here. I know it's unusual for a Commissioner to show up and stay for almost the entire meeting, but there are a couple of reasons that I'm interested in doing that and made the time, with the help of my staff.

This is occurring, I think, at the intersection of a lot of major societal issues that we're dealing with, the epidemiology of vulnerable populations for wounds, our soldiers and the elderly. I just heard on NPR yesterday that the over 65 crowd, which I'm just about to join, is going to double over the next 30 years, from 44 million to 80-something million

Americans. And, of course, we're increasingly seeing, both at home and abroad, wounds that are occurring for unfortunate reasons, having to do with war and related activities.

And then there are the concerns about evidence to support the use of medical products. We're in an era where we know that information is all over the place and growing rapidly, and how we turn that information into knowledge is a real challenge. And I think this is an area where it'll be fascinating to hear what the experts think about where we currently are in the eco-system that needs to produce the knowledge that we need to know how to use medical products effectively.

The third factor is more local. Many people know that we've been working hard on rejuvenating our approach to combination products at the FDA, and this is occurring in the epidemiology of medical product development, where we're hearing from many people that there's an enormous trend towards the development of combination products as a way of doing business.

And I think a simple way to think about this is if you just look at the embedding of computation into medical products of various types, there's a huge change afoot. And so we're going to have to understand better how to look at these combinations of medical products that are put together, each with their own baggage and opportunity that have to be dealt with as a composite.

And then an issue that I've been struggling with a lot, and I think all of our federal agencies are, and so is society as a whole, is antimicrobial resistance. And the question of how the products that are meant to deal with infection or prevent infection play into the issue of antimicrobial resistance is something that we've heard a lot of opinions about. It'll be important to get a sense today of what this Committee thinks about it, and whether and how we should consider it.

So it's exciting to learn from experts. It's fun for me to participate in a panel again. I

spent many years on FDA panels. To me, it's a place to bring together the best minds in a field and try to reach a common understanding. It'll help us evaluate a portfolio of over 700 products that need to be classified. I know you'll go through an exercise tomorrow. I won't be here for that, but very important part of your work. And it's an area of continued growth. We're seeing a proliferation of these products, and we need to understand how to regulate them as classes of products, in addition to the individuals.

And I hope we'll come out of this with a better sense of something that we're paying a lot of attention to and that we realize the FDA is only one factor in a very complex healthcare arena, where everyone is demanding better evidence. And it's incumbent upon us to figure out how to play our role in producing better evidence so that our labels are better and that people understand better what the best products are and how they should be used for the benefit of this rapidly growing population of patients.

So thanks, and I look forward to the rest of the day.

DR. HARRIS: Well, thank you very much, Commissioner Califf. So now to an overview of the combination products. The first presentation of the day will be given by Ms. Melissa Burns.

Ms. Burns, the podium is yours.

MS. BURNS: Thank you, and good morning. I'm Melissa Burns, a senior program manager in FDA's Office of Combination Products, and before we begin this specific discussion of wound dressings today, I wanted to provide an overview of combination products, both relevant terminology and some basic information on how FDA regulates these products.

So combination products are a distinct type of FDA-regulated product. They're composed of two or more different types of medical products. So this means they are drugs and devices, devices and biologics, biologics and drugs, or all three combined together,

drug, devices, and biologics.

The members of the Panel and the audience have likely come in contact with combination products. If you received a flu vaccine, for example, in a prefilled syringe, that would be combination product. Likewise, if you've seen first aid kits hanging on the offices in your buildings that contained devices and drugs, those would also be combination products

A term you may hear today, or in relation to combination products, is "constituent parts." What we mean by constituent parts are merely the products that comprise a combination product. The table at the bottom of the slide gives some examples. And to return to my previous example, with a prefilled vaccine syringe, in that case, the vaccine represents the biological product constituent part. The syringe represents the device constituent part.

Likewise, in first aid kits, the antibiotics or analgesics contained within that kit would be drug constituent parts, whereas gauze, tweezers, and other products contained within the kit would be device constituent parts of that combination product.

I'm going to rearrange, so hopefully that doesn't happen again.

The next term I'd like to introduce related to combination products is "mode of action." By their nature, combination products have multiple modes of action, represented by the contribution of each constituent part to the intended effect of the product. So again, returning to my prefilled syringe example, the drug within that product has a mode of action related to the therapeutic impact of that drug, whereas the device would have the mode of action of assisting in delivery of that drug into the body.

Combination products can be further characterized into "single-entity" or "co-packaged" combination products. By this we mean whether or not the product is chemically or physically combined, which would be the case for a single-entity combination

product, whereas products where the individual constituent parts are packaged together in the same package will be termed co-packaged combination products. For the purposes of this Panel meeting, we will be primarily discussing single-entity combination products, wound dressings that are embedded with or coated with drugs and other active ingredients.

So before I continue, I've told you what combination products are, but I also want to acknowledge a few product areas that can mistakenly be identified as combination products so that we provide some clarity here.

For example, when a product is comprised of two of the same type of medical product, that would not be a combination product. Examples can include fixed dose combination drugs or surgical kits comprised of multiple medical device instruments. Because those are the same types of products in the product, it would not be a combination product.

Another example of products that are not combination products are when you combine one medical product with one non-medical product. Examples in this case would be things such as lotions with sunscreen or cosmetics with sunscreens or medical foods. These would not be combination products because one of the parts of the product is a non-medical product.

Another area that may be of confusion is products that are separately distributed. For example, general use syringes, when they're distributed separately, and the vials of drugs or biologics with which they might be used would not be combination products. They would become a combination product if they were combined into a prefilled syringe presentation, or if a vial, for example, is co-packaged with a syringe.

So because combination products span multiple FDA centers, FDA has a mechanism for their review and assignment of a product to a given FDA center who has primary responsibility for their review. The center to which a product is assigned is termed the

"lead center," so you may hear that term as well today. The lead center is assigned based on which mode of action of the product provides the most important impact to the intended use of the product. And that is termed the "primary mode of action," or PMOA, another term you may hear.

For example, in the case of the syringes, because the biologic or drug contained within the product often is the primary contributor to the intended use, those products are typically assigned to CDER or CBER as the lead center for the combination product.

A lead center is also obviously responsible for collaborating with other centers in appropriately reviewing combination products.

To provide an example of PMOA, I have first a drug-eluting stent, which is a very commonly cited type of combination product. The PMOA for a drug-eluting stent is to hold open the artery, whereas the second mode of action may be related to the drug that's coated on the product to prevent inflammation or restenosis.

We contrast this with a drug-eluting disk. In this case, we assume the disk is coated with a chemotherapy agent. The PMOA in that case would be the drug coated onto the device. The secondary mode of action is related to that device delivering the drug to the intended part of the body. In the left side, or the drug-eluting stent, we would assign that product to CDRH as the lead center. Conversely, we would assign the drug-eluting disk to CDER.

I have provided additional resources on my slide for those who want more information. At this point, I'll turn over the presentation to Dr. Charles Durfor, who will begin with an introduction of wound dressings.

DR. DURFOR: Panel members, FDA staff, and visitors, good morning, and thank you for your attendance at this meeting that's discussing the unclassified pre-amendment medical devices collectively known as wound dressings combined with drugs.

In my presentation, I would like to first introduce each of the speakers and the topics from the Center for Devices and Radiological Health presentation today.

My name is Charles Durfor. I'm a bioorganic chemist by training and a senior scientific reviewer within the Plastics and Reconstructive Surgery Devices Branch 2, which is also PRSB2. PRSB2 performs the premarket review of wound dressing devices. My talk will also provide key definitions and identify some specific products that fall outside the scope of today's meeting. Finally, I will summarize a previous Panel meeting that was held in 2005 on this topic and why we believe the meeting today is very important.

I will be followed by Cynthia Chang, who is a biomedical engineer by training and serves as a senior lead reviewer within PRSB2. Her talk will cover both the current regulatory pathways for wound dressings as well as the type of data provided in 510(k) applications.

Brandon Kitchel, a reviewer also within PRSB2, who has joined the FDA after 8 years of research at the CDC on antimicrobial-resistant mechanisms associated with hospital-acquired infections, will also provide additional insight into the types of antimicrobial claims and evidence presented in 510(k) applications.

A clinical perspective on the serious types -- on the wounds under consideration today will be provided by Dr. Laura Marquart. She will also offer a summary of the recommendations and conclusions found in current clinical practice guidelines and the published medical literature. Dr. Marquart is a practicing dermatologist and a medical officer within PRSB2. She joined FDA after many years of private practice and military service.

Dr. Marquart will be followed by Karen Nast, who is a registered nurse by training and serves as a nurse consultant within CDRH's Division of Postmarket Surveillance. Ms. Nast will provide a provide a brief summary of the postmarket surveillance data

collected on wound dressings combined with drugs.

In the final CDRH presentation, Brandon Kitchel will provide a scientific perspective on the mechanisms of antimicrobial resistance and how it relates to different types of drugs present in wound dressings within procode FRO. He will offer some brief comments as well on the individual and societal implications of antimicrobial resistance.

To start, I'd just like to provide some clarifying definitions to help our discussions. Wound dressings combined with a drug may meet the definition of a combination product. In the previous presentation, Commander Burns from the Office of Combination Products provided insight into the definition of combination products and when CDRH might be assigned lead center review responsibilities for a wound dressing combined with a drug.

The term "pre-amendment medical device" means a product that was in commercial distribution before enactment of the Medical Device Amendments in 1976. For example, adhesive bandages containing boric acid and mercurochrome were commercially available as early as the 1920s and 1930s.

The final term is "procode." To assist in grouping similar products, CDRH has developed a series of product codes, or procodes, for each type of medical device. Thus the three-letter FRO is our shorthand for a group of medical devices that are wound dressings combined with drugs. In future talks, this grouping will be used to summarize the total number of premarket notification applications cleared and the MDRs submitted for these products.

In the next three slides, I'd like to help summarize some of the products we will not talk today. PRSB2 reviews a broad spectrum of wound dressings, and therefore it's important to know which ones are the focus and which are not.

In 1989 FDA proposed to classify interactive wound dressings as Class III medical devices. While the term "interactive" is perhaps not optimal, this group of products

includes any device that is a long-term or temporary skin substitute or prepares a wound for autografting. Thus, products claiming to accelerate the rate or improve the incidence of wound healing over the normal physiological condition or serve as a skin replacement prior to grafting, for example, dressings used on full thickness burn injuries, are Class III medical devices and are not the subject of this Panel meeting.

One example of this small group of products is Integra Omnigraft Dermal Regeneration Matrix, which was approved in January of this year, for improving the incidence of healing of partial and full thickness diabetic neuropathic foot ulcers.

Because these products are not a subject of today's Panel meeting, you will note that Questions 2 and 3 for your discussion this afternoon exclude the discussion of burns that might require skin grafting.

A second category of wound dressings that are not considered today are products that were classified in 1999. The definitions of these products are provided in Amendment 1 of your Panel briefing, and as a quick summary, they include non-resorbable gauze, external sponge, hydrophilic wound dressing, occlusive wound dressing, and hydrogel wound dressing.

It's important to note that the definition of each one of these products states, "This classification does not include products that contain added drugs such as antimicrobial agents, added biologics such as growth factors, or is composed of materials derived from animal sources." These products do fall outside the scope of today's meeting and are not combination products.

Finally, a third product which is not the subject of today's meeting is a wound dressing prepared with poly(diallyl) dimethyl ammonium chloride, or pDADMAC. In this dressing, pDADMAC, which is a highly charged polymer with antimicrobial activity, is permanently bound to the wound dressing. Because pDADMAC cannot leach from the

dressing material, this dressing is not a combination product, and once again, it's also not a subject for today's discussions.

In the next two slides, I'd like to briefly summarize the conversations that occurred in August of 2005 of this particular panel, the General and Plastic Surgery Devices Panel, on wound dressings with drugs and why FDA believes that hearing today from a second group of experts 11 years later is very important.

At this Panel meeting, FDA described the number and types of products cleared. They presented a summary of the safety profile observed in the postmarket setting and proposed a list of risks for product use and potential risk mitigation approaches that might serve as the basis for Class II special controls.

The Panel discussed factors such as establishing appropriate device descriptions and indications. Existing risks to health were also discussed, including antimicrobial resistance and the potential for patient sensitization. However, the level of AMR discussion in 2005 was limited, particularly based on what we know today. And the risks and mitigation strategies proposed did not identify AMR as a special control.

In addition, while the Panel considered the risks and benefits of the final product, the focus of the meeting was not on the specific risks and benefits associated with the drug present in the wound dressing.

At the conclusion of this Panel meeting, the Panel recommended Class II status for this group of medical devices. So why are we here today, and why is a second Panel meeting to discuss classification of wound dressings combined with drugs appropriate? Well, these products are still not classified. In addition, while FDA was preparing regulations to define these products and their appropriate indications for use, as well as the special controls that would mitigate risks and ensure product performance, considerable changes have occurred in the last 11 years, for example, in the area of product technology,

proposed indications for use, and risks to health.

For example, 87 products were cleared under the FRO procode between 2000 and 2005. In contrast, more than twice that number of 510(k)s, 196, were cleared between 2010 and 2015. This increase in premarket notification applications was accompanied by a number of potential new drug constituents and product claims. This is also reflected in the fact that while FDA presented a single definition for wound dressings combined with drugs at the 2005 Panel meeting, today we believe that three different definitions for wound dressings within the FRO procode are appropriate. Thus, we truly look forward to hearing your discussions on the scientific and clinical evidence available on wound dressings combined with drugs.

In my final slide, I'd like to sort of step back and give you an idea of the big picture of how we go forward, based on today's conversations. Today's meeting is focused on the clinical and scientific issues of wound dressings combined with drugs. Drawing upon these discussions, tomorrow you will discuss and recommend an appropriate class of medical device for wound dressings combined with drugs.

Following the meeting, FDA will review your recommendations and public comments to develop a proposed rule for device classification. This proposed rule will be published for public comment. Thereafter, FDA will review and consider the submitted comments and publish a final rule, classifying the products under procode FRO. A call for PMAs will be made for any Class III product.

At this point, I'd like to introduce Dr. Cynthia Chang, who will discuss the regulation of medical devices and wound dressings, as well as the information found in 510(k) applications. Thank you.

DR. CHANG: Thank you, Dr. Durfor, for the historical perspective on wound dressing regulation. Building on this important foundation, I will be discussing the current regulation

of wound dressings combined with drugs. As an introduction to my section of this presentation, I'll provide a brief overview of the topics I plan to cover. I'll begin with a discussion of the wound dressing classification paradigm before providing a more detailed description of wound dressings combined with drugs, which are the focus of this classification Panel meeting.

I will delineate the three subcategories of dressings, solid wound dressings; gels, creams, and ointments; and liquid wound washes. I will then provide a discussion of the 510(k) regulatory review process, which is a current review process for wound dressings with drugs. So with that, let's begin.

As you heard from Dr. Durfor's talk, wound dressings may be classified into Class I, II, or III, or they may be unclassified. The Class I wound dressings typically do not require premarket review, and the definition in the regulations specifically exclude products that include drugs, biologics, or animal-derived materials. These include the non-resorbable gauze and sponge for external use, hydrophilic, occlusive, and hydrogel dressings.

The Class II wound dressing containing pDADMAC additive is reviewed under the 510(k) premarket notification review pathway, which requires that a new product demonstrate substantial equivalence to a legally marketed device before it may be cleared for marketing. Class II devices are distinguished by the applicability of special controls, or specific requirements which are sufficient to mitigate the risks and provide reasonable assurance of the safety and effectiveness for that device type. I will discuss the 510(k) pathway later in this talk and special controls in more detail tomorrow.

Class III devices are subject to the most stringent device regulatory pathway, premarket approval, or the PMA pathway, which requires determination by FDA that there is sufficient valid scientific evidence to assure that the device is safe and effective for its intended uses. Generally, if a device is intended for wound treatment, intended for use as a

skin substitute, or is life-supporting or life-sustaining, then it would qualify for review under the PMA pathway as a Class III device. This means that if a device has claims for accelerating or promoting wound healing, it would be Class III.

Note that the wound dressings combined with drugs that we will be discussing are unclassified. This means that they do not fall into any of the three classes, and they do not have a classification regulation written for the specific device. The purpose of the classification process, which this meeting is part of, is to assign these unclassified products into Class I, II, or III, whichever provides the appropriate level of control for their risks, accounting for potential mitigation measures.

Tomorrow, Ms. Angela DeMarco will go over the definitions of Class I, II, and III in detail, and we will request that you comment on the appropriate class or classes for these products.

Please note that FDA does not believe it is appropriate to classify these products as Class I, considering the possible permutations of drug concentrations and combinations, because general controls alone are insufficient to mitigate the risks being discussed today. Therefore, we will be asking the Panel to concentrate on whether Class II or Class III will be appropriate for these products.

Currently, the unclassified wound dressings combined with drugs under product code FRO do undergo premarket review through the 510(k) pathway, as do all pre-amendment devices that do not have classification regulations.

I want to point out that there are other unclassified wound dressings that are outside the scope of this meeting as we plan to address them separately. These products include wound dressings containing animal-derived materials, such as bovine or porcine collagen, but do not contain drugs or biologics. Also outside the scope of this meeting are wound dressings combined with biologics, and wound dressings with or without an added

drug or biologic that are intended to provide a hemostasis through accelerated blood clotting when combined with manual compression. The focus of this meeting is on unclassified wound dressings with drugs under the product code FRO.

Wound dressings with drugs represent an active product area which includes over 700 510(k) submissions cleared to date. On the right hand side of the slide, you may see a graph of the number of submissions received and the number of submissions cleared each year in the FRO product code since 2000. As you can see, in the past 5 years or so, there have been approximately 30 to 40 new 510(k)s cleared annually.

This is in contrast to the situation in the early 2000s, when there have been approximately 20 or fewer clearances per year. Keep in mind that the number of 510(k) submissions does not correlate to the number of individual wound dressing products on the market as some submissions may cover multiple similar wound dressing products, or the submissions may represent modifications to previously cleared dressings.

The wound dressings within this product area may be subcategorized into three broad categories based on their physical form: solid wound dressings; gels, creams, or ointments; and liquid wound washes. I will take the next few slides to describe each group.

Solid wound dressings are composed of various synthetic or naturally derived materials and can be biodegradable or non-biodegradable. They can be in the form of a woven or non-woven fabric, pad, foam, or hydrogel that has sufficient structural integrity to hold a physical form, such as a scaffold or matrix. Some dressings are multi-layered, with each layer made of a different solid form, such as a four-layered dressing with a woven layer, foam layer, hydrocolloid layer, and occlusive adhesive backing layer.

The types of materials used in dressings include polyester, nylon, poly(vinyl alcohol), alginate, collagen, and various synthetic polymers. Typically, these dressings contain added antimicrobials such as silver, bismuth, chlorhexidine, polyhexamethylene biguanide or

PHMB, and bacitracin.

Solid wound dressings are generally intended for covering a wound, protecting against external contamination, absorbing exudate, and providing or supporting a moist wound environment. These dressings are typically cleared for use on a variety of wounds, including traumatic wounds; partial thickness burns; ulcers such as venous stasis ulcers, diabetic foot ulcers, arterial ulcers; or surgical wounds. These wounds may or may not be colonized with microbes.

Some dressings are cleared for use to cover and protect catheter insertion sites or other percutaneous device insertion sites, such as drains and orthopedic external pins. Some are cleared for management of infected wounds but not for treatment of infected wounds.

Gels, creams, and ointments are the next category of wound dressings with drugs. They are amorphous and can have high water content with thickening agents or consist of an oil-water emulsion. Many of these wound gels, creams, and ointments contain plant-derived materials, such as shea butter, avocado oil, or aloe vera.

These products typically contain added antimicrobials, such as paraben-based preservatives, silver, or PHMB. They are generally packaged in tubes or containers that can be for single use only or labeled for multiple use after the package has been opened. They may or may not be sterilized. I bring this up because products have been cleared with antimicrobials as preservatives to minimize microbial growth during shelf storage or multiple uses after the package has been opened.

However, products that do not contain antimicrobials are sometimes sterilized and labeled for single use. Here, I'd like to highlight that in Questions Number 1 and Number 5, you will be asked to discuss the utility of antimicrobials in dressings that are single use, multiple use with repeated opening of a container, sterile or not sterile, and the clinical

benefits of the associated claims.

Gels, creams, and ointments are generally intended for use to provide or support a moist wound environment. These dressings are typically cleared for use on a variety of wounds, including traumatic wounds, partial thickness burns, ulcers, or surgical wounds. Some products are cleared to relieve the symptoms of skin irritations, such as dryness, itching, and pain, by providing a moist wound environment. The types of skin irritations include various types of dermatoses, including radiation dermatitis and seborrheic dermatitis.

The third subcategory of wound dressings with drugs is a liquid wound wash group. Liquid wound wash solutions are typically water or saline-based. These wound wash solutions may contain various salts or surfactants. These products typically contain added antimicrobials such as hypochlorous acid, sodium hypochlorite, silver, or PHMB. They are generally packaged in bottles with plain caps or pump sprays, and they may or may not be sterilized.

Products have been cleared with antimicrobials as preservatives to minimize microbial growth during shelf storage or multiple uses after the package has been opened. Products that do not contain antimicrobials are sometimes sterilized and labeled for single use. Some products may contain antimicrobials but also be terminally sterilized.

Wound wash solutions are intended to rinse or irrigate a wound to physically remove foreign material, such as debris and wound exudate. Additionally, they have been cleared for physically irrigating away microbes, debris, and exudate from the wound. These products are typically cleared for use on a variety of wounds, including traumatic wounds, partial thickness burns, ulcers, or surgical wounds.

As mentioned in the previous several slides, a variety of drugs and additive ingredients have been present in cleared wound dressings under the product code FRO.

The examples mentioned previously are the most common or of particular interest to the discussion questions. However, please note that a more comprehensive list of the cleared ingredients is present in Appendix 2 of the Executive Summary.

For illustrative purposes, I present the entire list here. This is not an exhaustive list, but it provides a list of ingredients that either have or potentially have chemical activity, regardless of the intended function of the ingredient as described in the 510(k) submission. Note that while the majority of wound dressings products under product code FRO contain antimicrobials, there are wound dressings under this product code that contain other types of drugs, such as lidocaine and hydrocortisone.

The ingredients presented in Appendix 2 may be generally categorized into active ingredients and approved drugs, or drugs under monograph, such as bacitracin, chlorhexidine, iodine, hydrocortisone, and lidocaine. Keep in mind that drugs are approved for specific indications and in specific forms that may be different than those represented in FRO products.

Chemicals may be identified as inactive ingredients in approved drug products, such as benzalkonium chloride, calcium carbonate, glycerol, methyl salicylate, or parabens; other chemicals with antimicrobial activity, such as crystal violet, hypochlorous acid, ozone, or silver; plant-derived material and botanical extracts, such as aloe vera, oak extract, and tea tree oil; and other additive components, including salts, surfactants, and thickening agents, such as betaine, chromium chloride, ceramide, and sodium tetraborate.

Please remember the diversity of drugs and ingredients present in cleared wound dressings when you answer Question Number 4 regarding the risks of systemic toxicity and absorption this afternoon.

Now that we've discussed the products in question, I'd like to explain how they are reviewed by FDA before they may be introduced on the market.

The 510(k) process is the informal term for the premarket notification regulatory review pathway, which is how wound dressings with drugs are currently reviewed prior to marketing. This process involves the evaluation of substantial equivalents of a new product or subject device compared to a previous legally marketed device or predicate device. The new product must be found substantially equivalent to the predicate device prior to marketing through a hierarchical decision-making process.

In general, the 510(k) process is based on the assumption that for a group of products, we have reasonable assurance that the devices are safe and effective for their intended uses. This determination may be made through classification of the products.

For unclassified pre-amendment products, new devices are compared to pre-amendment predicates, those that were already in commercial distribution prior to 1976. However, in the case of these unclassified pre-amendment products, we have not made a formal determination regarding their risks and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness, and that is the purpose of this classification Panel meeting.

Generally, the review process examines the intended use of the devices to ensure that even if there are differences in indications and labeling, that ultimately, the intended use of the new and predicate device are the same.

For cleared wound dressings, we consider a broad sense of intended use when making that comparison, such as intended uses of covering and protecting wounds, maintaining a moist wound environment, and rinsing a wound. Likewise, the technological characteristics of the subject device are compared to the predicate device to determine if they are the same. And if they are not the same, we evaluate whether the differences raise different questions of safety and effectiveness.

In evaluating the technological characteristics, we consider the composition and

ingredients in the dressings as well as the concentration and amount of individual components. If the differences in technology raise different questions of safety and effectiveness than those we asked for the predicate, which would require different types of evaluations or specific testing compared to the predicate, then review could not continue down the 510(k) pathway.

Once the same intended use and the same or similar technology are shown, only then may review of specific testing and data begin. If the test results demonstrate equivalent performance, then the subject device is substantially equivalent to the predicate, and it may be legally marketed.

I'd like to note that as outlined in CDRH's 510(k) program guidance, the principles of safety and effectiveness underlie the substantial equivalence determination in our 510(k) review process.

As you can tell from the previous slide, the typical content for a 510(k) submission reviewed by FDA includes a complete device description, the indications for use statement, draft labeling, and testing to demonstrate substantially equivalent safety and effectiveness as compared to the identified predicate device.

The types of testing regarding safety include a toxicological risk analysis and biocompatibility evaluation for potential cytotoxicity, irritation, and sensitization response. Depending on the material composition and topological risk analysis, additional biocompatibility evaluation, such as chronic toxicity, systemic toxicity, or genotoxicity testing may be necessary.

Animal or clinical studies to evaluate product effectiveness are not always needed to demonstrate substantial equivalence. Animal testing is sometimes requested by FDA to demonstrate that wound healing is not delayed due to use of the wound dressing product. Clinical studies to evaluate product safety are not typically necessary but can be conducted

to evaluate biocompatibility response, such as irritation and sensitization in human subjects.

Clinical studies may be needed to support substantial equivalence for certain indications, such as a reduction in the incidence of catheter-related bloodstream infections. Please keep this in mind as you consider Questions Number 1 and Number 5 regarding the types of data required to support marketing of these products.

Additionally, product performance testing is provided, depending on the characteristics of the device. Such data typically consists of bench testing, such as tests demonstrating the ability of dressing material to absorb fluids or to minimize water loss through dressing material. Material strength testing may also be conducted.

Because the components in wound dressings are generally sensitive to degradation during shelf storage, data to support shelf stability has also generally been necessary to show substantial equivalence. And for products that contain antimicrobials, testing regarding antimicrobial effectiveness is conducted, which you will hear about in the next section of the FDA presentation, delivered by my colleague, Brandon Kitchel.

With that, I will turn the lectern over to Mr. Kitchel, who will discuss the specific antimicrobial testing that is evaluated for these products.

MR. KITCHEL: There we go. Good morning, and thank you, Dr. Chang, for your presentation. My name is Brandon Kitchel, and I'm a microbiologist in the Center for Devices and Radiological Health. For this next talk, I'll be discussing performance claims and the supporting testing that are typically submitted for wound dressings containing antimicrobial agents.

As a brief overview, I will begin by providing background information on the framework for antimicrobial performance claims cleared in CDRH. I will also provide a simplified example of a microbiology test setup, including common features that should be

considered for most performance testing. Next, I will discuss the importance of establishing the minimum effective concentration of antimicrobial in a wound dressing. And finally, I will outline the types of performance claims that are currently reviewed in unclassified wound dressings, accompanied by the most commonly submitted supporting test methods.

For the purposes of this presentation, these performance claims have been grouped into what we currently refer to as preservative claims, antimicrobial claims, and microbial barrier claims.

To begin our discussion, the following background information may help provide context as to what claims are considered appropriate for antimicrobial wound dressings. First, please note that all antimicrobial performance claims cleared in CDRH are limited to an action within the product, and any claim regarding effectiveness on microbes in the wound would need to be reviewed by the Center for Drug Evaluation and Research.

The vast majority of performance claims are based on in vitro testing data. And although animal or clinical studies may be requested by the Agency, they are not typically needed to demonstrate substantial equivalence to a previously cleared predicate device.

Currently, the Agency does not recognize any in vitro antimicrobial effectiveness testing standards that can be directly applied to antimicrobial dressings without modifications. As a result, it is the sponsor's role to define what testing is appropriate for their product. To assist with this process, sponsors are encouraged to submit performance testing protocols via our presubmission process to receive preliminary feedback from the Agency.

For the majority of claims, supporting test protocols should generate quantitative results based on colony counting and log reduction analysis. Regarding log reduction analysis, for those who are unfamiliar with microbiology test methods, I have outlined the following six steps to give an overview of a general protocol.

First, it's important to define the test article, which should be the final product at the end of the stated shelf life. Additionally, if testing is to support a product's performance while in use, the test articles should be conditioned to emulate factors of clinical use prior to testing.

Next, the test article is inoculated with a clinically relevant test microorganism. Depending on the claims and test methods, selection of a broad set of test organisms should account for microbial diversity and should include both gram-positive and gram-negative bacteria, along with species of yeast and mold.

Third, the inoculated dressing is then incubated for a specified period of time, which is either based on the stated use life of the dressing or is outlined in a reference testing standard.

For the fourth step, surviving test organisms are extracted from the test article using a neutralization buffer. This buffer eliminates lingering effectiveness of any antimicrobial which may have leached away from the product and into the solution.

Fifth, extracted microorganisms are serial diluted and plated for colony counting, using standard microbiology techniques as described in United States Pharmacopoeia Reference Standard 61.

And for our sixth and final step, log reduction is calculated. This log reduction calculation subtracts the viable organisms recovered after treatment from the viable organisms before treatment. For those unfamiliar with a log scale, please note the corresponding percent reductions here.

Acceptance criteria is established depending on the performance claims and should be stated in the supporting test method protocol.

Prior to testing, it's important to establish the minimum effective concentration, or MEC, of antimicrobial in a wound dressing. For those familiar with clinical microbiology or

in vitro drug efficacy testing, please note that MEC is equivalent to MIC, which measures a drug's minimum inhibitory concentration.

The concentration of antimicrobial within a wound dressing is critical to both the product's safety and performance. Too high of a concentration could lead to safety risks, such as biocompatibility issues and delayed wound healing, both of which will be addressed by Dr. Laura Marquart in the next presentation. However, too low of a concentration may compromise the overall antimicrobial performance of the product. Defining the MEC is an important parameter for manufacturers as the concentration of antimicrobial should be sufficient to maintain the stated effectiveness of the wound dressing throughout its use life.

MEC testing typically involves producing a series of decreasing concentrations of antimicrobial in preliminary test product. For example, this photo shows a serial dilution with antimicrobial concentrations ranging from 64 µg/mL down to 1. After inoculating each product with test organism and incubating overnight, the lowest concentration that met the acceptance criteria is identified as the MEC. In this example, 8 µg/mL would be considered the MEC as it appears to be the lowest concentration that successfully hindered microbial growth within the test solution.

I will now focus my talk on the types of performance claims and supporting in vitro testing that are commonly seen for wound dressings containing antimicrobials. Please note that the majority of performance claims are not supported by clinical data, and as a result, overall clinical relevance of these claims is unclear. This is a major topic of discussion as part of this meeting, and I would like to remind the Panel that you will later be asked to discuss the clinical relevance of these performance claims along with the types of supporting data that should be provided as part of Question Number 1 of the provided Panel questions.

For the purposes of this presentation, performance claims have been distilled down

to the following three main categories: First, what we currently define as preservative effectiveness claims addresses microbial growth within a product while on the shelf. Next, what we currently define as antimicrobial effectiveness claims addresses microbial growth within a dressing while it is in use. And finally, what we currently define as microbial barrier effectiveness claims addresses microbial penetration through a dressing, also while it's in use.

Jumping right into it, I will now discuss preservative effectiveness. Preservative effectiveness claims mostly apply to products such as wound gels, creams, and ointments along with wound washes and irrigation solutions. The rationale for including an antimicrobial agent in these products is either to improve the shelf life of a non-sterile product or to permit repeated openings and multiple uses of a container after the sterile seal has been broken. Please note that these claims do not typically apply to solid wound dressings as these products are primarily single use and sterile devices.

Preservative effectiveness claims that have been cleared in CDRH include "maintains a low bioburden during shelf storage and after repeated openings of the package," along with "inhibits the growth" of species of microorganisms, which may include drug-resistant strains.

For preservative effectiveness claims, one of the most commonly applied test methods is USP <51>. This testing includes inoculating the liquid or gel product with the listed five test organisms, which respectively includes one gram-positive bacterium, two gram-negative bacteria, one yeast, and one mold. The inoculated product is then incubated for periods of 7, 14, and 28 days, after which surviving organisms are extracted. No controls are included in this test method, and log reduction analysis is based on the starting inoculum concentration.

Acceptance criteria for topically used products with aqueous bases, which are

Category II products as defined in USP <51>, include greater than or equal to a 2 log reduction at day 14, and no increase at day 28 for bacteria, and no increase from the initial count at days 14 and 28 for yeast and mold.

Moving on to antimicrobial effectiveness claims, which again pertain to performance while the product is in use, antimicrobial effectiveness claims have primarily been cleared in solid wound dressings which include an antimicrobial agent to reduce bacterial colonization of the dressing while in use. Please note that these claims do not typically apply to liquid and gel-based wound dressings as in-use performance claims regarding these products may imply a delivery of antimicrobial action to the wound.

Some examples of antimicrobial performance claims that have been cleared in solid dressings include "an antimicrobial effect to minimize microbial contamination or colonization of the dressing," "kills a broad spectrum of bacteria, including MRSA and VRE, within the dressing," and "provides sustained antimicrobial activity in the dressing for up to 7 days."

For antimicrobial effectiveness of solid wound dressings, one of the most commonly applied standards is the AATCC Test Method 100, which assesses antibacterial finishes on textile materials. Requested modifications to this standard include having a broader selection of test organisms, including at least three gram-positive bacteria, three gram-negative bacteria, one yeast, and one mold species.

The test article should be a swatch of the finished product, as defined in the standard, and should be conditioned to emulate factors of clinical use prior to inoculation. The inoculated dressing is then incubated for various periods of time from throughout the product's use life. Additionally, test results should be compared to an appropriate material control, such as the subject dressing without the antimicrobial component. This is important to factor in percent recovery of test organisms during log reduction calculations.

Acceptance criteria to support antimicrobial claims should be greater than or equal to a 4 log reduction for each test microorganism.

A critical component to antimicrobial effectiveness testing is factoring in emulated use conditions in order to add a degree of clinical relevance to in vitro test results. This conditioning typically includes soaking the product with simulated wound fluid for a specified period of use in order to condition the dressing for potential interfering factors, such as temperature, pH, soiling, and protein deposition.

Additionally, the excess simulated wound fluid will maximize the amount of antimicrobial that may potentially leach away from the dressing and compromise the overall minimum effective concentration.

In our final category, I will now discuss microbial barrier effectiveness claims and supporting performance testing. Microbial barrier claims have primarily been cleared in solid wound dressings that are either primary dressings, meaning they interface directly with the wound, or secondary dressings that provide additional covering or help secure a primary dressing.

The rationale for including an antimicrobial agent in these products is to provide a barrier against microbial entry into a wound. This may be achieved by either a physical barrier that denies passage through the material or by an antimicrobial barrier that relies on a biocidal activity to eliminate microbial penetration.

Examples of microbial barrier claims include "covers and protects the wound," "a barrier to penetration of microbes to the wound, which may reduce the risk of infection," and "to enhance the microbial barrier function and minimize growth of microbes in the wound dressing."

Typical performance testing to support microbial barrier claims include the following experimental setup: A sterile conditioned dressing is first placed on an agar plate with

growth media. Subsequently, the top of the dressing is inoculated with $1x10^6$ CFU of a test organism. After a specified period of time to support the product's use life, the dressing is removed, and the agar plate is incubated to examine for penetrating microbial growth.

Typically, this testing is performed with a reduced number of test organisms. However, it's critical that these organisms include motile species of bacteria which contain mechanisms of propulsion, such as flagella that aid in their ability to travel through the dressing. The test article should again be the final age dressing that has been conditioned based on emulated clinical use.

It's important to include both a positive and material control in this testing to confirm that the barrier properties are attributed to the antimicrobial within the dressing. Unlike preservative and antimicrobial effectiveness testing, this is a qualitative assessment as we are only looking for growth or no growth of penetrating organisms.

Thank you for your attention. Now I would like to welcome Dr. Laura Marquart, who will be providing a clinical perspective on unclassified wound dressings containing antimicrobial agents.

DR. MARQUART: Great. Good morning, everyone. So I'll be talking about the clinical perspective of these unclassified wound dressings. To give you an overview, I'm first going to be talking about the types of wounds that would be used on these dressings, the guidelines and clinical studies that have been performed on these products, and then the indication for use statements that we have cleared for these products.

So first we break it down into acute wounds and chronic wounds.

I don't think it's coming up on the big screen.

And so, with acute wounds, we think acute wounds occur suddenly, and then they heal at an expected rate. We think of acute wounds as post-surgical wounds, lacerations, or burns, and then they can be as minor as an abrasion, a scrape on the knee, or as serious as,

you know, as a burn. In this discussion, we won't be talking about full thickness burns. So these would be partial thickness.

And then the next type of wounds we'll be talking about are chronic wounds. Chronic wounds, the most common type of chronic wounds we see are venous ulcers, diabetic ulcers, pressure ulcers. And these are wounds that occur over time and then do not heal at an expected rate. And any acute wound can go on to become a chronic wound. So chronic serious wounds are the types of wounds that we would be using these products on.

And as you can see, this is just some causes of leg ulcers that can be chronic serious wounds. There are many types of wounds, and so we have many types of dressings for use.

The next thing we're going to talk about is wound management, so where do these dressings fit into the management of these wounds? Of course, initially, we want to control the bleeding. Then we want a clean wound, and this is where a wound wash may come into play. We would debride the wound, and then we would use a dressing to cover and protect the wound, and a dressing or cream or gel would come into play here. We take pressure off the wound, so we offload the wound, especially in diabetic foot ulcers or venous ulcers or pressure ulcers. And then we may use antimicrobials, topical or systemic.

So the next thing that I'll be talking about are the clinical practice guidelines. So now that we have seen the wound dressings, we're going to discuss these. And the next few slides should help you address Questions 1 and 2 that we have for the Panel.

This is a summary drawn from the Executive Summary, and it includes both U.S. and world guidelines. We recognize that international guidelines, they may have a different practice of care, but our intent was to be all-inclusive. This chart is broken down by wound type, the source of the recommendation, and if an antimicrobial dressing was recommended or not.

Over the next few slides, I'm going to be going through the different wound types and talking about the source of recommendation and then the recommendations for it.

So for the first one, the diabetic foot ulcer, this came from the Infectious Disease Society of America, the International Working Group on Diabetic Foot Ulcers, and the International Consensus on Diabetic Foot Ulcers. And all of these guidelines do not recommend antimicrobial wound dressings.

For venous leg ulcers, we have some difference of opinion. There's three guidelines from the Society of Vascular Surgery, the Australian and New Zealand Wound Care Society, and the Scottish Intercollegiate Guidelines do not recommend antimicrobial dressings. However, the Expert Working Group, an international group from Harding, and then the Canadian Association of Wound Care state that there may be certain circumstances where antimicrobial dressings may be used, to include short-term management of wound infections in conjunction with systemic antibiotics.

So the next type are pressure ulcers. And for pressure ulcers, from UK's National Institute for Health Care Excellence, their guidelines, the Canadian Association of Wound Care, and the National Pressure Ulcer Advisory Panel, they recommend to consider using an antimicrobial dressing where clinically indicated. And then an example they give is if there's a spreading cellulitis or in areas of high risk for contamination.

For wounds in general, again we have a little difference of opinion. The UK National Institute for Health Care Excellence and the American Society of Plastic Surgeons, they do not recommend the use of antimicrobial dressings. Canadian Association of Wound Care and the Wound Healing Society recommend judicious use in certain clinical situations. They say to consider a 2-week trial of topical antimicrobial dressings if the wound isn't healing despite optimal care.

And the next type of wound we come across are burns. And this is from the

American Burn Association. And they recommend against the use of prophylactic antimicrobials to protect against cellulitis or sepsis, that there is no evidence that topical antimicrobial agents in minor burns can reduce the incidence of infection.

The next one are catheter insertion sites, and this comes from CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections. They do recommend the use of chlorhexidine-impregnated sponge dressings for temporary, short-term catheters, if the central line-associated bloodstream infection rate is not decreasing despite adherence to basic preventive measures.

So now we change gears a little, and we talk about, in this group of products, there are also some that don't have antimicrobial but have other ingredients, and that's where we talk about atopic dermatitis. And from the American Academy of Dermatology, they state that the application of moisturizers are an integral part of treatment of patients, that there is strong evidence their use can reduce disease severity and the need for pharmacologic intervention.

And the things that we talk about in this group are the topical moisturizers, so these are the creams, gels, or ointments. And in topical moisturizers, we have petrolatum, dimethicone, lactic acid, and urea. And then there's these prescription emollient devices that contain ceramides or filaggrin breakdown products. And those are also ones that you would be looking at in this group of dressings.

And so this just shows that chart again. So catheter insertion sites are the only "yes" recommendation at this point, from these guidelines.

The next thing that we're going to look at is the clinical literature review. And this was conducted with a goal to assess clinical evidence supporting the use of antimicrobial dressings over non-antimicrobial dressings, to prevent or treat wound infections or to improve wound healing.

And again, this is a chart drawn from the Executive Summary. It goes through the type of wound, the source of the recommendation, and the antimicrobial dressing conclusion that was made. Some of these sources are from Cochrane Reviews, which are systematic reviews of primary literature. And as I go through each type of wound, I'll go through the types of literature that were looked at.

So for the first one, for the diabetic foot ulcer, this came from a 2015 review from Uckay, and then also a 2013 European Wound Management Association systematic review. This was Level 1a and b evidence. And they said that no topicals demonstrated superiority. You know, the review looked at over 350 patients. And so there was little evidence to support the choice of any one dressing over another, in preference, to promote the healing of chronic ulcers of the foot in diabetic patients.

So for venous leg ulcers, this one was a Cochrane, a 2014 Cochrane Review, with Level 1a evidence. It was 45 studies, with over 4,000 patients. And some studies suggest antimicrobial dressings improve wound healing. And one of the ones they discussed was iodine, but there were more frequent adverse events, which I will talk about at the end, while other studies suggest that they do not. And then some studies found inconclusive results.

The next one is for pressure ulcers, and this was from a 2016 systematic review. This was Level 1a and b evidence. There were 12 studies, and over 576 patients. And from that, they said the data was too limited to draw any conclusions in terms, and the data was limited because of study size, study design variations, and study duration.

For the next one, wounds in general, there is a 2008 systematic review with over 14 studies, 1,000 patients. This was Level 1 and 2 evidence, to assess the effectiveness of these dressings. And they found that silver dressings may lead to some improvement; however, there is variability in the methodology and confounding factors, like systemic

antibiotic use, so that it limited the conclusions that could be drawn from the data.

For burns, this was from a 2013 Cochrane Review of over 30 Level 1 evidence, and they looked at the effects of burn wound dressings on wound healing. They looked at silver and chlorhexidine, hydrocolloid and silicon, and there were no differences in wound healing.

For catheter insertion sites, there were two Cochrane Reviews from 2016. The first was Ullman's review, with 22 Level 1a randomized control trials. And they demonstrated that medication-impregnated dressings reduced catheter-related bloodstream infections. However, there was an increased risk of skin irritation.

The next systematic review was by Lai, in 2016, and they focused on neonates and found that antimicrobial dressings, compared to control dressings, did result in significant differences in catheter-related bloodstream infections, with these patients especially having a higher rate of irritation from these products.

And so here's that chart again, to summarize. So there are few well-designed randomized control trials to support one dressing type over another dressing type. The major flaws include small sample sizes, inappropriate control groups, not defining the types of patients or wounds, dressings that were made with different materials, inconsistent use of terms and definitions of infection, and the concomitant use of oral antibiotics. And that's what makes these dressings a challenge.

As we did this literature review, we did find there were general safety concerns that have been reported that we'd want to address, and they included delayed wound healing with silver or iodine, toxic reactions with some of these products, irritant and allergic reactions, and of course, antimicrobial resistance.

So now we're going to change gears, and we're going to be talking about indications for use statements for these products. And this may help you to address Question

Number 5.

So our indication for use statement on our products identifies the condition and the patient population. They're normally indicated for prescription use; however, some products can be cleared for over-the-counter use on minor cuts, scrapes, or abrasions. They may be cleared for use on infected or colonized wounds, but they are not to replace the standard methods for treatment of infected wounds. And these products are not cleared to treat infected wounds. The language or terminology that we've seen -- Dr. Chang addressed this in her talk -- but that these are to cover and protect, absorb exudate, or create a moist wound environment, and then for the wound washes, to rinse debris.

So clinical studies for these devices are typically requested by the FDA when bench and animal testing aren't sufficient to support the claims, when new technology differs from the cleared product, and where indications for use for the product, when there's a new indication for use for the product. And those are when clinical studies may be requested.

So now we're going to go through some examples of each of these types. So we'll start with wound washes, go to antimicrobial dressings, and then go to the creams and gels.

So this is a representative indication for use statement. It uses the language, you know, cleansing and removal of foreign debris, and then it talks about the condition or patients that this would be used on, so for this specifically, the types of wounds.

The next indication for use statement is for an antimicrobial dressing. This one also gives a duration of use, how many days it can be used. And this one is very, it's short. It just talks about the types of wounds that it can be used for. And that's in contrast to the next one for antimicrobial dressings.

This one talks about the duration of use, the types of wounds it can be used on, and then there's some terminology to include that this provides an antimicrobial barrier, a moist wound healing environment, management of painful wounds. So this is questions we ask

you. Are these clinically meaningful to the patient or to help the provider?

And the next one is a representative indication for use for a catheter or a port dressing, port site dressings. These are to absorb exudate, to cover a wound. They describe the types that they would be used on. And then this one has specifically to reduce local infection, catheter-related bloodstream infection, and skin colonization. Now, in contrast to the others, there was actually a clinical study that was included with this, to get these indications for use, where there was over 500, almost 600 patients. And they did show a statistically significant reduction in bacteria. And so that's how they were able to get this labeling.

And then the last one is a representative indication for use for a cream. And so this goes back to the atopic dermatitis, so that we think of atopic dermatitis, radiation dermatitis. There's allergic contact, seborrheic dermatitis. And these are to manage symptoms of the skin disease, such as burning, itching, and pain. And then also they talk about relieving the pain of first and second degree burns.

So hopefully I was able to provide some framework to address some of these questions that we present to you today. And now I turn the mic over to Karen Nast, who will be talking about the postmarket analysis that's been done.

MS. NAST: Thank you, Dr. Marquart. I'm Karen Nast, a nurse consultant in the Division of Postmarket Surveillance in CDRH. I'm going to provide an overview of the MDR data for product code FRO.

This slide provides a brief reminder of the limitations of MDR data. Each year, the FDA receives over a million MDRs reporting suspected device-associated deaths, serious injuries, and malfunctions. The FDA uses MDRs to monitor postmarket device performance, detect potential device-related safety issues, and contribute to benefit/risk assessments of devices.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including under-reporting, data quality issues like the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. The limitations of the MDR regulation: A lack of MDRs does not necessarily mean there are no problems. It is not possible to definitively determine a causal relationship between an event and the device based on MDR data alone. Finally, the incidence or prevalence of an event cannot be determined from this reporting system alone, due to potential under-reporting of events and lack of information about frequency of device use.

The MDR database houses MDRs submitted to the FDA by mandatory reporters, including manufacturers, importers, and device user facilities, as well as voluntary reporters, such as healthcare professionals, patients, and consumers. For the purposes of this analysis, the MDR database was searched on July 28th using the FRO product code with no date restrictions. Using the search criteria, we identified 1,125 relevant MDRs.

The number of MDRs received each year under product code FRO since 1994 is shown. 1,010 reports were submitted by the manufacturer or distributor, 78 reports were submitted by voluntary reporters, 37 reports were submitted by user facilities. There were 623 reports from the U.S. and 502 reports from outside of the U.S.

There were 17 death reports, 725 serious injuries, and 383 malfunctions. To summarize the 17 death reports, in 5 of the reports, the manufacturer concluded they were not likely related to the device; for the rest of the death reports, the manufacturer could not determine if the death was related to the reported device. The cause of death was provided in nine MDRs. The patients' cause of death, as reported, include septic shock, sepsis, infection, fentanyl intoxication, severe pulmonary arterial hypertension, and cardiac decompensation.

Each report was individually reviewed to determine the patient problems. The most

reported patient problems include erythema, infection, and blisters. Keep in mind that it is not always clear from the MDR if the reported patient problem is a result of the device or if it was already present.

Each report was individually reviewed to determine the device problems. The most reported device problems are packaging issues, foreign materials present, and difficulty removing the dressing from the patient.

In conclusion, in the past 22 years, 1,125 MDRs have been received for product code FRO. The most commonly reported patient problems are erythema, infection, and blisters. The most commonly reported device problems are packaging issues, foreign materials, and difficulty removing the product. The 17 reported deaths could not be conclusively linked to the use of the device.

Thank you.

DR. HARRIS: Thank you.

I'd like to thank all of the FDA presenters and actually ask them to please come take a seat at this table in the front for a bit of an inquisition on behalf of the Panel members. This will be a time now for any clarifying questions that the Panel members may have.

I'd like to also remind the Panel members that you also ask questions of the sponsor in addition to the presenters from this morning. So any questions?

Dr. Sayeed.

DR. SAYEED: Dr. Sayeed. The FDA makes a good case to regulate many of these medical devices on your presentation as Class III devices, which would require a PMA and a clinical trial. If, let's say hypothetically that, you know, we advise the FDA to regulate these devices as Class II devices, what assurances could you give the Panel that special controls would be in place -- and I know you're probably going to talk about this tomorrow, but I just want to pose the question today -- that could mitigate some of the adverse risks that we've

talked about this morning, including fatalities from devices; i.e., would labeling guidance, you know, documentation for postmarket surveillance -- on paper, they look great, but do physicians read those labels? Do the companies follow the documentation that the FDA provides? I think these are major, major things that we need to talk about, and this is a major conversation that we're having today.

Also, you know, we talked about antimicrobials. One thing that the FDA did not talk about today, so far, is the preservatives. There's a lot of preservatives in a lot of these devices. What do we know about the toxicology? Are there nanoparticulates?

I was just on a Panel meeting in April, and there was a concern that the particular device was leaching chemicals into the body, which caused heterotopic ossification. And we never really heard, you know, from the manufacturer about what the risk was for that. And so, you know, if the FDA could comment on that at some point over the next couple of days, that'd be great. Thanks.

DR. CHANG: So I believe your question was in two parts. And for the first question, I'm Cynthia Chang, and I'll answer that question. And for the second one, regarding preservatives and toxicology, Dr. Charles Durfor will answer that question.

So the first question was regarding, I guess, if the Panel recommends Class II versus Class III. Please note that the FDA is not making a recommendation at this time as to whether the devices or groups of devices should be in Class II versus Class III. We are really interested in hearing your thoughts and perspectives on the risks and potential controls that could be available to regulate the devices in either Class II or Class III.

That said, if the Panel recommends Class II, and we issue a proposed rule regarding Class II, then we would have the opportunity to write special controls, which could be very broad, regarding the requirements for controlling and mitigating the specific risks for these devices. They could be broad, such as requiring biocompatibility information, or they could

be very specific, requiring specific performance testing or even clinical or postmarket surveillance studies.

And so that is really dependent on the feedback that we receive from you today, from the public comments in the docket, and public comments that would be received after writing the special controls and the proposed rule. So we are really interested in hearing your thoughts as to, you know, whether the risks to health could be mitigated through special controls. That said, there are methods that are available to us, to be very specific in labeling, to require postmarket surveillance or, I guess, registration and listing for these devices.

DR. DURFOR: Thank you for your question about preservatives. In your briefing packet, we gave you a list of all the products that were there. Some are recognized preservatives, things like parabens. Some are different. And in terms of particulate, in terms of tissue toxicity, those are important concerns.

And so the way we generally deal with that, with a product, is actually we look at each product through the 510(k) process. We see where the material is sourced from so we know what impurities might be in it. We look at the concentration of material, the preservative or the antimicrobial that is there, and see how that concentration compares to previous products, because obviously concentration is a key factor, as you heard from Mr. Kitchel.

We then also have a battery of biocompatibility tests, such as cytotoxicity, sensitization, guinea pig sensitization, and an irritation assay. And we look for those sort of factors as well. And a manufacturer, of course, would give us specifications for their product. So we would have a sense of what is the physical form of the material.

In the case of any of the biocompatibility tests, most likely cytotoxicity, giving us a concern, then we routinely ask manufacturers to take the next step and to look at a porcine

wound healing model, pigs being perhaps the best animal model to approximate human skin, although there's probably no animal model that's perfect. But then to use that model, to look at how a product that might be cytotoxic, how does it impact the process of wound healing, particularly in comparison to a control and a predicate device?

DR. ALAM: Thank you all for your talks. They're very informative and very clear, and that was very much appreciated.

One issue that you raised, I believe several presenters raised, was the evidence, the clinical evidence in support of using antimicrobials for specific indications. And in doing so, you reviewed some guidelines. And you also reviewed some systematic reviews, specifically Cochrane Collaboration reviews.

One of my concerns, which I'd like for you to address, is that there seems to be a little ambiguity there in the case of the reviews. There is some -- sorry, in the case of the guidelines, there's some supportive, some non-supportive in some cases. And I'm concerned that we shouldn't necessarily conclude that there's no evidence, or that the absence of a consensus doesn't mean that there's nothing there. So that's one concern. I was hoping you could address that.

And then with regard to Cochrane reports, those of us who are -- I'm sure most of those of us in this room who read those routinely are aware that the Cochrane Collaboration, because of its very strict methodology, frequently results in conclusions that are very hedged and often highly inconclusive. I mean, I think I can certainly envision -- and I'm not trying to be facetious -- a Cochrane report that assesses whether jumping out of windows causes people harm and finds that there are no randomized control trials to substantiate that. And as a consequence, they're unable to make any determination whether that's a harmful activity.

I'm not trying to be facetious, but they are applying rigor. But as a consequence of

that rigor, sometimes when important studies haven't been done, the implication can be that they don't work or certain techniques don't work. But often it's just a matter of certain studies not being done. So I'd very much appreciate your thoughts as to how you sifted the evidence to make sure that the absence of good data wasn't taken to mean that certain processes weren't valuable.

DR. MARQUART: So I can start to answer this, and if anyone else wants to go after me, they can. But that was, you know, the difficulty with this. So our review, when we looked at everything, we tried to be all-inclusive, but you know, regardless of that, we can't get every bit of data. And there's some guidelines that do say, this may be helpful with short-term use, and that some guidelines, you know, don't recommend it.

The data -- I understand where you're coming from with the Cochrane Reviews. So some of them were Cochrane; others were just, you know, systematic reviews that we drew for some of the diseases. And it's difficult to -- the thing that we kept getting back, we did a further one even after this where we just looked at U.S. guidelines. So this one contained international and U.S., and then we looked at U.S., and we have this, very similar results, that there's not a lot, there's not a lot of great randomized control trials. There are some. And some find that they are beneficial, and some find that they're not. And so we wanted to present, you know, the evidence that we had, so --

DR. SOOD: Thank you for your great presentations. They were truly terrific. I'm Geetika Sood. I wanted to ask you sort of along the lines of what Dr. Alam had said. The absence of data is obviously not the same as negative data.

More specifically, regarding the clinical trials that were presented, when you combine a lot of patients together and try to do a randomized trial, which we tried to do, related to wound microbiome, with so many patients, the subgroups get lost in that process.

In your review, were you able to find certain subgroups, which is what you would hypothesize, would benefit most from antimicrobial dressings that did, in fact, benefit?

DR. MARQUART: So that's why I broke it down by wounds, you know, by wound type on that chart that we drew because there are some, like the venous leg ulcers, the pressure ulcers, and then wounds in general when -- in terms of in general, they also include post-surgical wounds or -- but there was, you know, some evidence to say that there was some benefit.

We found, with burn, you know, burn wounds, it didn't seem to be any. But so we did look at subgroups, specific, yes, subtype.

DR. HARRIS: Please turn your mic on.

DR. SOOD: Sorry. I would suggest that we may even need to look at more specific subgroups, like infected leg ulcers versus non-infected leg ulcers. So that may be a place that may be of benefit.

May I ask a second question? Thank you.

My second question was related to the antimicrobial effectiveness testing. It looks like there are certain organisms that you have to have two gram-positives and two gram-negatives, as you had recommended. If a particular sponsor wanted to just go for gram-positive coverage or a more specific antimicrobial efficacy testing, is that something that's possible?

MR. KITCHEL: Thank you for that question. The short answer is yes. The sponsors are really defining how their product functions and what claims they want to make regarding that product's function. If they only want to claim that it is effective against gram-positive organisms, they could limit their claims accordingly, to say that this will hinder the growth of gram-positives within their product.

Typically, we like to ask for a broad spectrum as these reagents have a broad

spectrum of effectiveness. So we would like to see a more diverse population of organisms to be tested. But defining those specific organisms does fall on the responsibility of the sponsor, and we're happy to provide feedback during that process. Thank you.

MS. LOTT: Hi. Michelle Lott. I'm the Industry Representative. I've got three questions; two are kind of related.

Early on, you guys spoke to the substantial equivalence paradigm and comparing it to other legally marketed processes. What would be the impact on the substantial equivalence paradigm of any outcomes of the decisions or recommendations that this Committee may make? You know --

DR. DURFOR: I'll try and answer that, and if I don't, please follow up. In one of my slides, I tried to show you how today and tomorrow's meeting played into the overall process. So we've heard, as well, that the Cochrane Reviews and the like don't always -- you know, we're looking to your comments. I think that's my underlying sense, is that your discussion today is very important, that your discussions tomorrow are important. And then we will factor that into our review with public comment, go forward with a proposed rule, and there'll be chance for another public comment.

So at this point, I think we're kind of at the beginning, and that we really want the best science and the best medicine from you today, and that the impact on the review process is a bit farther down the road.

MS. LOTT: So the second part to that question is I know that recently another FDA committee on the drug side had made the decision to remove, I believe, 19 antimicrobials from hand soaps. And the products on the market have a certain period of time to phase those ingredients out. Is that a potential outcome of this meeting for products that are already on the market, that the industry would have X period of time to either present data or to remove those, or what's the status of the product that's currently legally marketed?

DR. DURFOR: I'm not exactly sure on your question, so I'll try and answer it again as best I can. So I'm not going to comment on the drug aspect. We have our colleagues from Drugs here, should you have specific questions.

But I do think those sort of actions are, once again, down the road, that what we're really interested in today is just your clinical experience, your scientific experience, and what's right. And then from that, we'll move forward as a science-based agency.

DR. CHANG: I just want to follow up on that. So we had talked a little bit about how tomorrow we'll be asking the Panel about classification into primarily Class II or Class III. Should the Panel recommend Class III, and we choose to go ahead with a proposed rule for a Class III for some of these products, then there would be a call for PMAs for any products in Class III. And in that case, there would be, I believe, 30 months from the date of the proposed rule for products that would fall into Class III to submit PMAs.

MS. LOTT: This is my last one, my third part. In the literature review, you mentioned there were several cases of a maybe situation. Say the wound's not healing within a certain period of time, then, you know, start -- I don't want to say experimenting -- with antimicrobial agents to see if you can improve the speed of wound healing.

Now, how would this Panel go about making recommendations? Because that gets more into standard of care and maybe practices within a particular hospital facility that are kind of outside the scope of anything a manufacturer could put in a indication or that the FDA could put in a guidance document. How would those types of things roll into the outcomes here?

DR. CHANG: So with the indication for use statements, those are, you know, the guidelines that the FDA propose, you know, proposes, puts out for the manufacturers for their labeling. And there is a difference, though, with the practice of medicine, as you say. And each individual patient, each individual wound is treated differently. So it's really up to

that physician how they are going to practice and how they're going to use that dressing.

DR. HARRIS: Dr. Ashar.

DR. ASHAR: Yeah. I had a couple of comments. I think what you've heard from the FDA team is that the information that you have that we've presented is somewhat ambiguous because the data is ambiguous. And this is a challenging product area for that reason.

And what we're doing today, by convening this panel, is really looking for your input. We don't know how we should classify these devices. We want to do the right thing, and we want to classify them as either a Class I, II, or III. We think that Class II or III may be the most appropriate place, but we're really looking for this Panel to advise us.

So the question is, is should more studies be done? If not, what evidence exists today for us to make recommendations on how to regulate these appropriately? What should the endpoints be if the studies are conducted? And, you know, how can we ensure that manufacturers, as they label these devices, are communicating what testing has been performed, what the evidence does show and what it does not show?

So, you know, our FDA team assembled this information, trying to be as even-handed as possible, recognizing that there's not a lot of good evidence, you know, for this challenging product area. So hopefully that gives you some perspective.

And if we proceed, you know, thoughtfully today and answer the scientific questions, it's our hope that when we come to making some -- the Panel comes to making recommendations regarding how we should classify these, we'll be able to pull from today's discussion to have this Panel make informed decisions for tomorrow.

MS. KRUEGER: May I clarify just the process pieces in response to Ms. Lott's comments.

DR. HARRIS: Can people please state their name before making their comments?

Thank you.

MS. KRUEGER: Sure. Angela Krueger, Associate Director for Guidance and Regulations in the Office of Device Evaluation at CDRH. And what you saw from Dr. Durfor was the process steps. And he did mention that this is the first step in our classification process. And what CDRH will do, and the Agency will do, in terms of next steps is a proposed rule, taking into account your considerations and your recommendations here today.

In terms of the timeline -- and it would not have any effect on products that are currently marketed today -- as that proposed rule goes out, as we consider those comments, what would be actionable is the final rule that would be subsequent to the proposed rule.

In both the proposed and the final rule, we would outline an implementation strategy for how we would manage products that are currently on the market and future products. And there is some discretion for the Agency in how we do that. And we consider marketed products, the companies, and the impact on public health as we take those actions.

As Dr. Chang mentioned, we would subsequently do a call for PMAs if any of the products were to be classified as Class III. And that would be a coordinated effort with the proposed rule and the call for PMAs. What the statute says, related to that final action, is that a company with a currently marketed product would have 30 months at the time of that final rule to submit a PMA.

We would review the PMA, and then a decision would be made regarding whether or not those products would have to come off the market based on that independent dataset. Should a firm not submit a PMA within that time frame, if they are classified as Class III, then they would have to cease marketing.

DR. HARRIS: I think, Dr. Holmes, you had a question. Then we'll get everyone.

DR. HOLMES: Just to -- Jimmy Holmes -- just to clarify your interpretation of the ABA CPGs, in the burn world, when we talk about prophylactic antibiotics, that's systemic. It's not topical. And so, you know, we've got to be careful not to mix the two. Not only that, when we talk about minor burns, they really are minor. I mean, they're minimal. So what they're talking about, having and making a recommendation about not requiring topical antimicrobials are something just a little more severe than sunburn.

Excuse me, one last comment. In looking back at the archived Panel minutes from 2005, you had absolute unanimity of the Panel to classify all of these devices as Class II. That was 11 years ago. What happened?

DR. DURFOR: Thank you for that question. As I mentioned in my talk, we listened to what was said. We read the public comments and all that went with the docket for that. We began to prepare a regulation. We began to think through what are the appropriate special controls? And things were just changing. I think you saw that today. There were new products, new constituents, new indications for use. I think that Ms. Nast's talk showed that there was an increase in MDRs. And so we were coming to grips with that.

But I think really the bottom-line question is science and medicine has moved forward in the last 11 years. I don't there's anyone at this table who would disagree with that. We've looked at the data. We've tried to present that to you today, and it just seems appropriate to come back to this Panel and say, okay, 2005, this is what we knew; 2016, this is what we know now; what's the right thing to do?

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Dr. Durfor, Bill Hickerson. Question for you along those lines: When you're talking about your MDRs, you've listed basically 51 per year. And some of those, when you look back at those, are difficulty removing the dressing, things of that

nature, which would seem to be more user error than product error, where you get an ingrowth of tissue, which may indicate that it was left on too long.

And when you look at that, how many products were actually used per year, that would then give you an incidence, per chance, of those?

MS. NAST: Thank you for your question. Karen Nast. That is a limitation of our MDR database. We are not able to establish incidence.

DR. DURFOR: Oh, I apologize. Just to reiterate, that one of the things, I think, that's very important about the MDR presentation is just alerting to people the importance to report these. And I really appreciate that.

As Ms. Nast said, we know neither denominator, which is how many products were sold and used, or the numerator, how many events occurred, because of under-reporting. So it's a challenge to try and derive incidence or percentage data from the events. But I do think, overall, if you take it for what it's worth, there is information there. I think the question you've raised is a good one. And I don't have a better answer.

You want to speak more about what you've got? No? Okay.

So at this point, I'm not sure how to answer your question other than to acknowledge its value.

DR. HARRIS: Dr. Burke, do you have a question?

DR. BURKE: Yes, thank you. I'm Dr. Karen Burke at Mount Sinai Medical Center in New York, a dermatologist. I first want to say that the whole, all of the presentations were excellent and very clarifying. I just want to clarify the 510(k) specifications, which seem to have very excellent criteria, with biocompatibility, absorption testing, sterility, and certainly the antimicrobial tests that Dr. Kitchel mentioned, the three categories. And perhaps we should extend some of those testing to include more gram-positives or gram-negatives, etc.

So, first, I just wanted to ask if every drug applied to these dressings has already

been FDA approved as a medication. So if everything, every component was already approved, that's of great importance. And it just seems that those criteria are -- maybe we would modify the criteria a bit, as we said, by microbial testing and preservative testing and preservative leaching and preservative concentration.

So I think maybe extending those criteria are good. But the criteria seem very strict. And also, even though we have many, many new medications, I mean, the number has gone up by a factor of four that were -- are tested, only 60% have been approved by the 510(k) criteria.

So, first of all, I want to commend the FDA for those excellent criteria. And it seems that possibly we should just think about modifying those criteria in our overall discussion, because they are incredibly excellent.

MS. KRUEGER: This is Angela Krueger, CDRH. I'll start, and if the Division has additional thoughts --

Related to your question regarding the different types of antimicrobials and their status, as it relates to FDA's review of those specific antimicrobials, and what we outlined in the talks and in our Executive Summary is that some of these antimicrobials may truly be and meet the definition of a drug. There may also be antimicrobials that don't meet the definition of a drug, depending on their particular use.

And so it may be, for example, that for a preservative or another use, they wouldn't be considered in the future combination products. And we'd be looking closely at that. And I think, if the Panel has comments on that, we would certainly appreciate it.

What we do know, for some of those products, depending on intended uses, is that the drugs may not be approved for the specific use in these dressings, under the specific conditions of use or indications for use as they're defined for use in these dressings. And so we would also appreciate the Panel's input regarding if there are particular types of

antimicrobials or particular uses combined with a wound dressing that you believe there are specific concerns about, that we highlight those and call them out in today's discussion and tomorrow's discussion.

I think we will be looking at the status of the products in the buckets that Dr. Chang outlined as we look at the antimicrobials and how they're used.

DR. HARRIS: Dr. Wolf.

MR. KITCHEL: If I could, if I could quickly add to that. No worries. Brandon Kitchel. Thank you for your comments. And we agree that, you know, your thoughts on extending testing to include more gram-positive and gram-negative organisms, you know, it makes sense as clearly there's a tremendous amount of diversity in bacterial species. And even within certain species, we know that there's incredible diversity there as well.

So based off of the predicate system, this is kind of the formula that we've been going with as far as what we're asking sponsors to provide. But if there were future questions or opportunities, we do appreciate that thought.

And just one quick point of clarity: You had mentioned the word "medication," and previously there was a comment regarding systemic versus topical antibiotic use. And I just wanted to clarify that. While the purpose of those products, medications and antibiotics, would be to treat infections, to kill bacteria in wounds, really we're talking about antimicrobials in wound dressings with a different intention, right. We're talking about maintaining a low bioburden within those products.

So I just wanted to make sure to clarify that. So thank you.

DR. WOLF: So Steve Wolf from Dallas. Some comments on the literature stuff that you did: You know, as I told you, I see a lot of stuff that maybe doesn't reach the light of day. And it's frustrating for us in the burn world and in the chronic wound world and some of these other places is that what we're trying to do is very difficult to measure. And so

what you end up measuring is things that you can measure, but those things don't always matter.

So, for instance, you talked a lot about wound healing, the rate of wound healing, and I agree with you. There's probably not much difference, right, with antimicrobials. In fact, I tell my medical students and residents all the time is that these are antibiotics. It turns out we're biotic, too. And so that everything probably limits the wound healing.

So but that's not the only thing that matters, right. And if you look at these products that have come out, such as the silver dressings in burns, have been rapidly, rapidly incorporated into our practices such that they're now the standard of care. And why did that happen? Not because of wound healing. It's because of patient satisfaction probably. Right? And but that's not in the literature, is it? Right, because it's difficult to measure.

And so my plea is to make sure that we consider that. I know you guys will. I'm just getting it on the record, right, that sometimes we measure what, you know, we can when what we can't measure is what actually matters.

Further, the other issue is that I agree with you there's probably not a whole lot of risk of infection. The problem is when an infection occurs, it's a fat tail. And that tail can include death. And if it only happens one in a thousand times, well, are you going to be that one in a thousand?

And that's a problem with the data in that just the way we set up studies is we're looking for differences when you can't find the tail, and you know, there's the, you know, the black swan effect and all these other things that people talk about. So I encourage you to also consider that -- and I know you will -- in your considerations, and in our considerations. And, you know, you're asking for commentary, so I'm giving it to you, right.

And so then finally, I want to mention as a, you know, a practitioner and as someone who is involved in clinical trials, if I had to do, you know, if I was asked to do a PMA study,

I'm going to compare Silvadene to, you know, one of these silver dressings, I don't think I can do it, right. Because it's clear to us clinically why these products have been so rapidly adapted is because of patient satisfaction. And now we're going to -- so the problem is now our control group is going to get what we think is less than the standard of care.

DR. HARRIS: Any response from the Panel? No.

DR. MARQUART: No, we appreciate your response and understand that. And that's what we do take into account, and that's why we're asking like are these indication for use statements clinically meaningful? You know, the evidence that we presented, is it clinically meaningful to the patient?

DR. HARRIS: Commissioner Califf?

DR. CALIFF: Yeah, I have four questions, so if you all can try to keep responses short in the interest of time, I appreciate it. First of all, just thanks for the tremendous work. You've heard from the Panel that your presentations were very good and clarifying. I just want to ask a question related to the AE reporting and incidence.

Based on everything I've learned since coming to the FDA, spontaneous adverse events are a critical part of our effort, but what would you say the rate of spontaneous reports would be compared to what's actually happening in practice? I'm guessing a small fraction.

MS. NAST: Thank you. Karen Nast. It's really hard to say. One of the limitations is under-reporting, and you know, our data is what -- we get what we get. We've had 1,125 MDRs over 22 years. I can't talk --

DR. CALIFF: Hard to put it -- so just a comment on that. I mean, this is the reason, as you know, that we're trying to put together a systematic assessment tool called the NEST for devices because otherwise it's almost impossible to calculate numerators and denominators. I see you nodding your head, so it was a leading question.

The second one is, I think, is a much tougher one. Typically, in therapeutics, when you look at equivalence, you're comparing something new to something old that's been carefully studied. And you know, as I look at this, it reminds me of what happened with drugs prior to 1962, when you had a lot of things on the market. They'd never been studied. We had the thalidomide disaster -- and there's no disaster here, so I'm not making that comparison -- but you let Congress pass a law saying you got to look at things that are on the market, is there evidence to support them?

And what I'm asking your perspective on is if most of these things were on the market prior to the 1970s, they probably weren't very systematically studied in the first place. So we're then making an equivalence determination compared to something that never was established as being effective in the first place. Is that a correct assumption? And what does that mean?

DR. DURFOR: You're right. That's a difficult question.

(Laughter.)

DR. DURFOR: The way the medical device law works is that with pre-amendment products, they were grandfathered in. And if they were in commercial distribution and remained in commercial distribution, there was a sense that they had some value.

But your concern is real, and I think that's why there has been a very strong emphasis for all pre-amendment products that are unclassified to go through this process, to step back, to say okay, fine, now let's look at the data, now let's see what's here. Let's see if we got it right, and do the data suggest where we should go?

DR. CALIFF: Okay. Then the third question is maybe even tougher. You know, I'll just, you know, comment that it's been a very difficult thing, I think, for the whole FDA and all the federal agencies to try to understand what to do about antimicrobial resistance. You know, we now have a law that essentially tells farmers they can't put antibiotics in the feed.

And when I go out on the stump with farmers, they say, well, you're not doing anything with these doctors who are proliferating hospitals and nursing homes with antibiotics.

And I know there are many complexities here, and this afternoon, the Panel will have a chance to talk with all the experts here, so this question is just directed at you. Has antimicrobial resistance been a part of the evaluation of these products up until now? And just in your view, based on what you've looked at, are there any hints you would give us as we have the discussion this afternoon about how to consider the societal implications?

MR. KITCHEL: Thank you very much for that question. Antimicrobial resistance is clearly a serious public health concern, and up to date, this has not been factored into the 510(k) review for these products. Clearly, as we've already mentioned, these are pre-amendment products dating back to 1970, and the landscape of what we knew about antimicrobial resistance then to what we know about it now is quite different.

And so we do appreciate your question and comment, and I'll be talking about antimicrobial resistance and potential mitigations for that in my next talk after break.

Thank you.

DR. CALIFF: The last, number 4, this thing about evidence -- you know, and again, it'll be, I think, a fascinating discussion this afternoon with the Panel about how to weigh clinical experience versus objective evidence, but I'm sort of interested in two parts of it.

One is, as you look at the ecosystem in this area, there are obviously areas of devices where clinical trials get done routinely in a very efficient fashion. You know, I'm thinking of coronary stents as an example where that happens, and others, where in a presentation like this, what you really said was we just don't know. That's my interpretation of your excellent literature review. And I'm sort of interested in your view for a later Panel discussion this afternoon about are there things that could be done to get higher quality evidence?

And then the second part was stimulated by Dr. Wolf's point; you know, it's been fun for me to see how CDRH is taking patient preferences as a really important part of labeling and consideration. Let's say a dressing was no better than or lacked clear evidence otherwise, but it really was better for patient satisfaction. Would patient preference be a consideration in this arena?

DR. DURFOR: I'll try and start with your last question first. Patient-reported outcomes are important. But they're balanced against the risk that the product presents. And so patient-reported outcomes alone, it depends, obviously depends on the product area. And in this product area, there are other clinically relevant out points that also have to be taken into consideration. So patient-reported outcomes, patient preference are important, but they're balanced against truly what is the product doing for the patient as in a clinical sense, and what risk does it present?

And your first question, I'm sorry. I'm going to ask you to repeat it. I apologize.

DR. CALIFF: I think we'll have probably a robust discussion this afternoon about why we don't have better evidence and whether -- I'm judging by some of the points made by the Panel already, that some may feel we don't need more evidence because clinical experience is enough. But what are your sort of hints about what you'd like to see happen with evidence?

DR. DURFOR: I'm going to start, and maybe Dr. Marquart would want to finish. I think that is the real reason we're here is to hear from the experts in terms of what they think is appropriate. And that's really why we have them here. But I would suggest that this organization is not alone, and there are many other organizations out there, we heard, with guidelines, that are also not only saying we need better evidence but outlining the ways trials can be done.

And as someone who's been fortunate enough to work in this area for a long time, I

recognize that these are not straightforward trials. The endpoints, some are simple, some are not. But wound dressings is only one part of a greater picture. So getting homogeneity in terms of patient subgroups, to get equivalent groups, to take into consideration the other confounding factors, sometimes which are more important than the wound dressing, such as diabetic ulcers need offloading, and the wound dressing only plays a part.

In chronic wounds, there's issue with patient retention in studies. So these are challenging studies. And it's not to belittle your question but to recognize the landscape we live in.

DR. HARRIS: One last -- oh.

DR. MARQUART: Right. This is Laura Marquart, and I agree with Dr. Durfor. And we actually have -- Dr. Gottrup is going to be speaking after the break and discussing, you know, endpoints, what might be more beneficial or -- because I think it's hard to say what evidence.

And I think as we talked about pre-amendment, you know, those things were on the market. They may not have been studied well, but there was some obvious benefit to it. And then that's what we're comparing. And so now, you know, what are the dressings that do have some benefit, and would they need clinical studies? That's what we're asking the Panel.

DR. HARRIS: One last quick question, Dr. Miller.

DR. MILLER: Okay, thank you. I just am looking forward to some guidance from you in how to consider a question like antimicrobial resistance because it's an unusual sort of question, it seems, in a forum like this where we're not looking at individual patients or group of patients. We're looking at more of a global consideration. So how do we weigh that when we think about these questions that we're looking at with classifying these devices?

MR. KITCHEL: Thank you for your question. And you're absolutely right. I'll be discussing both the impact on a patient level and on a society level. But antimicrobial resistance, it's a big topic. It's a big issue. And, in fact, today the United Nations is actually meeting to discuss it, you know, on a global level. So clearly it needs to be addressed. And hopefully I'll do a good job later today and be able to provide some insights on antimicrobial resistance and how it relates to the products at hand for today's Panel. And I look forward to your questions after that presentation.

DR. HARRIS: Thank you. So we're now going to take a short break. I'd like to remind the Panel members to please not discuss the meeting topic during the break amongst yourselves or with any other members of the audience. We'll take 19 minutes for our break, and please reconvene at 10:40. Thank you.

(Off the record at 10:21 a.m.)

(On the record at 10:40 a.m.)

DR. HARRIS: It's now 10:40, so we're going to resume our meeting. I'd like to call us back to order. At this point, we will now prepare to hear Part 4 of the FDA's presentations. I'd like to once again remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel chair.

We begin now with Dr. Kim, who's going to make some additional clarifying comments provoked by our earlier discussion.

DR. KIM: Thank you, Dr. Harris. My name is Peter Kim, and I'm a medical officer in the Center for Drugs in the Division of Anti-Infective Products. And I was asked to make a couple of clarifying comments.

So I think we should be aware that there are differences between an indication for a drug for the treatment of infectious disease versus the indications provided for the Center

for Devices for an antimicrobial combined with a device, such as a patch. So when that drug is in with the patch, my understanding is such indications may include that the drug is there as a preservative or to prevent contamination versus how a drug might be studied in the Center for Drugs, for the treatment of the actual infectious disease.

So even if a drug is approved in the Center of Drugs, when it comes over in a combination product in the Center for Devices, it's actually a new entity for presumably a new indication, such as for preservative effect or for prevention of contamination. I think it also should be noted that some drugs may not actually be approved in the Center for Drugs as well.

Any questions at all? Thank you.

DR. HARRIS: Thank you, Dr. Kim.

So now we'll hear again from Brandon Kitchel.

MR. KITCHEL: Okay. Thank you, Dr. Kim, for that clarification. And welcome, everyone, back from break. Again, my name is Brandon Kitchel, and I'm a microbiologist in the Center for Devices and Radiological Health.

For this next talk, I will be discussing the benefit/risk considerations for including antimicrobial agents in wound dressings.

As an overview for my talk, I will begin by giving a brief background on antimicrobial usage and the development of antimicrobial resistance. Subsequently, I will outline the different categories of antimicrobials currently utilized in wound dressings and provide information on their historical usage, mechanisms of activity, and known bacterial resistance. And finally I will present both benefit/risk considerations that may have impact on both an individual patient and societal level.

Prior to getting started, I would like to remind the Panel that you will later be asked to discuss the value of using these antimicrobials, the risk of antimicrobial resistance, and

the factors which should be considered when determining clinical benefit of these products as part of Questions Number 1, 3, and 5, with the provided Panel packet.

Antimicrobials have been implemented on multiple levels in a concerted effort to curb clinical infections and transmission of pathogens in a healthcare environment. This includes the systemic or localized use of antibiotics to treat bacterial infections; along with antiseptics, such as skin wipes and wound sprays; and disinfectants, such as cleaning supplies.

Since their discovery by Alexander Fleming in 1928, there have been numerous classes of antibiotics developed to attack specific bacterial targets. This figure provides a nice overview of these various classes of antibiotics and their synthetic counterparts, along with their respective bacterial targets.

Antiseptics and disinfectants are both broad-spectrum biocidal agents that are either applied on living tissue or inanimate objects, respectively. Some common examples of antiseptics and disinfectants include benzalkonium chloride, chlorhexidine, alcohol, and hydrogen peroxide. It has been noted that proper antiseptic and disinfectant usage within hospitals is considered the most appropriate first line of defense and can minimize reliance on antibiotics.

It's important to understand that each antimicrobial is only effective for a limited segment of the microbial world. Some bacteria species are naturally resistant to a particular antimicrobial, while others may acquire resistance via either random genetic mutation or acquisition of an entire resistance gene.

Many resistance genes are found on mobile elements of circular DNA called plasmids, and these plasmids play an integral role in the horizontal transfer of resistance between strains of bacteria. Additionally, it's well known that multiple resistance genes can stack together on a single plasmid.

For example, this figure shows a plasmid that was sequenced from a strain of *Klebsiella pneumoniae* and contains resistance genes to mercury along with multiple classes of antibiotics, including carbapenems, macrolides, aminoglycosides, beta-lactams, and quinolones.

Decades of antimicrobial usage has contributed to the selection of bacteria with a vast array of antimicrobial resistance mechanisms, including the expression of hydrolytic enzymes, activation of efflux pumps, and the decreased permeability of outer cell membranes, just to name a few.

In addition to bacterial resistance mechanisms, the presence of biofilms in a clinical setting also adds to the overall level of antimicrobial resistance. These are polymicrobial communities which adhere to a surface and secrete a matrix of extracellular material that complicates the availability of an antimicrobial and provides opportunity for shared resistance mechanisms between species.

The overuse and misuse of antibacterials has contributed to the cultivation of an abundance of drug-resistant organisms that are becoming increasingly difficult to treat. And the CDC reports that each year in the United States, over 2 million people become infected with drug-resistant bacteria, and at least 23,000 people die as a result of these infections. Taking all of this into account, it's clear that the development of drug resistance is a serious public health concern, and there is a need for improved antimicrobial stewardship practices to preserve the efficacy of our current antimicrobials.

Now I will focus my talk on the use of antimicrobials in wound dressings. In this section, I will cover the main categories of antimicrobials used in wound dressings and provide details on their historical uses, along with the mechanisms of activity and known bacterial resistance. However, I would like to note that although resistance mechanisms to these types of antimicrobials has been reported in the literature, little is known about their

prevalence.

There are four main types of antimicrobials that have been cleared in wound dressings, including metal-based antimicrobials, quaternary ammonium compounds, oxidizing agents, and biguanides.

For metal-based antimicrobials such as silver and bismuth, these are historically one of the oldest types of antimicrobials, and medical usage can be traced as far back as 1500 B.C., to ancient Egyptian times. Metals have been used for the antimicrobial properties in water disinfection, food preservation, agriculture, and medicine throughout history. However, focus had shifted away from metals after the discovery of antibiotics.

Currently, metals such as silver are used for coatings on medical devices, including endotracheal tubes, embedding on personal protective equipment, such as surgical masks, and as part of the water disinfectant process employed by NASA.

The bactericidal mechanism of action of metal-based antimicrobials is believed to be a result of metal cations binding to thiol groups in cell membranes and the deactivation of critical bacterial enzymes. Additionally, metal ions may interact with nucleic acids, although it's unclear how this interaction may impact the overall lethal action.

Known resistance mechanisms have been observed in select species, including some gram-positive organisms that have developed modified cell walls with increased peptidoglycan thickness, which may retain positively charged silver cations, in addition to plasmid-mediated efflux pumps.

Quaternary ammonium compounds (QACs), such as benzalkonium chloride, have been historically widely used as both antiseptics and disinfectants. In the healthcare environment, QACs are commonly used for sanitation of non-critical surfaces such as floors and walls. Additionally, EPA-registered QACs are appropriate for disinfecting patient-contacting medical equipment, such as blood pressure cuffs.

The accepted mechanism of action of QACs is that of a cationic surfactant, which binds by ionic and hydrophobic interactions to cell membranes, causing a loss of membrane integrity and overall cellular disruption.

Known resistance to QACs has been observed in select species, including the prevention of QAC uptake by gram-negative outer membrane lipopolysaccharides and plasmid-mediated efflux pumps which have been observed in select gram-positive organisms.

Oxidizing agents, such as hydrogen peroxide and hypochlorous acid, have historically been used as both antiseptics and disinfectants. Three percent hydrogen peroxide is commonly used as an over-the-counter wound antiseptic, in addition to being used for both teeth whitening and bleaching hair. Also, chlorine-releasing agents, such as household bleach, are widely used for hard surface disinfection.

The bactericidal mechanism of action of oxidizing agents is believed to be a result of the production of free radicals, which then attack essential cell components, including lipids, proteins, and DNA. Also, chlorine reacts with amino groups and irreversibly oxidizes sulfhydryl groups, which inactivates essential bacterial enzymes, crosslinks proteins, disrupts lipid bi-layers, and interferes with DNA-based pairing.

Known resistance to oxidizing agents has been observed in some gram-positive strains, which produce catalase or other peroxidases that increase their tolerance while under lower concentrations.

Finally, biguanides, such as chlorhexidine and the polymeric biguanide PHMB, have been historically used as disinfectants and antiseptics. In 1970 chlorhexidine was first commercially introduced in the U.S. as a disinfectant and topical antiseptic. Subsequently, chlorhexidine has been used to coat a number of medical devices, such as catheters and sutures, and chlorhexidine baths are common infection control practice recommendations

made by the CDC. PHMB has also been used as a disinfectant and antiseptic in many products, including those for cleaning contact lenses.

The bactericidal mechanism of biguanides is believed to be that of a cationic interaction with the first layer of the membrane phospholipids, which subsequently affects membrane fluidity and confirmation. Additionally, polymer strands of PHMB are able to incorporate into and disrupt bacterial cell membranes. Biguanides are also known to bind to DNA, alter transcription, and ultimately cause lethal damage to nucleic acids.

Known resistance to biguanides has been observed in select strains, and mechanisms of resistance include the production of mucoexopolysaccaride in certain mucoidal strains, which may reduce biguanide diffusion, along with the presence of plasmid-mediated efflux pumps.

Based on this information regarding types of antimicrobials in wound dressings, we can draw the following conclusions: Antimicrobial agents previously cleared in wound dressings have historically been used as both disinfectants and antiseptics. These reagents have bactericidal mechanisms that attack multiple bacterial targets, which may contribute to their broad spectrum of activity. Although known resistance mechanisms have been observed in select organisms, little is known about the prevalence of these resistance mechanisms without conducting future surveillance studies.

For the third and final part of my talk, I will now discuss some potential benefit/risk considerations regarding the use of antimicrobials in wound dressings on both an individual patient and societal level of impact.

Potential benefits to an individual patient may include the following: Preservatives in gels, creams, ointments, and washes may ensure the safety of these products by hindering growth of potential contaminating organisms. Barrier properties of solid wound dressings may help cover and protect wounds from the environmental introduction of

opportunistic microbial pathogens. And microbials in -- sorry, antimicrobials in wound dressings may help to reduce bacterial growth within the dressing, which may become a nidus for infection if the dressing is infrequently changed or has prolonged use. Please note that you will be asked to discuss these potential patient benefits, including if they are clinically meaningful, as part of Panel Question Number 5.

As you have previously heard from Dr. Laura Marquart and Ms. Karen Nast, some potential risks to the individual patient may include biocompatibility issues, such as sensitization, irritation, and cytotoxicity, along with allergic reactions or delayed wound healing. Each of these risks have been observed, to some degree, with a number of antimicrobials found in wound dressings, including silver, chlorhexidine, PHMB, and hypochlorous acid. In addition, please note that in 1998, the FDA issued a public health notice regarding potential hypersensitivity reactions to chlorhexidine-impregnated devices.

Some additional potential risks to the individual patient may include the impact of unnecessary usage of antimicrobials, which may condition the normal host microflora, killing off commensal organisms and potentially increasing susceptibility to opportunistic species. Also, the selection of antimicrobial-resistant strains may select for co-resistance to antibiotics and other systemic antimicrobials, making it more challenging for clinicians to prescribe future therapeutic interventions.

Potential benefits on the societal level may include leveraging antimicrobial agents that have been previously established as antiseptics and disinfectants to curb the growth of microorganisms on or in medical devices, such as wound dressings, which may help reduce our ultimate reliance on systemic antimicrobials to treat bacterial infections.

Potential societal risks with the use of antimicrobials in wound dressings may include the impact on future development and spread of antimicrobial resistance mechanisms. Also, it should be noted that selection of resistance to antimicrobials in wound dressings

may select for co-resistance to classes of antibiotics. As a result, the application of one selective pressure may force bacterial strains to maintain plasmids with multiple resistance mechanisms, even in the absence of systemic antibacterial drugs.

As a final note, antimicrobial stewardship practices have been recommended to maintain efficacy of our currently available antimicrobials. On September 18th, 2014, the White House issued an Executive Order regarding antimicrobial stewardship measures to reduce the emergence and spread of antimicrobial-resistant bacteria and recommend a more judicious use and proper disposal of our current therapeutics. This is important considering that it's estimated between 20 and 50% of prescribed antibiotics may be unnecessary or inappropriately used. HHS has been engaged in efforts to promote antimicrobial stewardship practices and curb the spread of antimicrobial resistance.

On that note, I would like to introduce our next presenter, Dr. Finn Gottrup, who will provide a more detailed clinical perspective on the potential benefits and risks of using antimicrobials in wound dressings, in addition to discussing wound care considerations on an international level.

Dr. Gottrup is a gastroenterologist and surgeon from Denmark. He is the recipient of the North Carolina Nielsens honorary award, a member of the European Tissue Repair Society, the European Wound Management Association, and the Danish Wound Healing Society. Dr. Gottrup has served as an editor of numerous journals and textbooks and is well published in the field of wound care. Thank you for your attention.

DR. GOTTRUP: I hate to stay in a panel. For this reason, I am standing here. I want to be able to move around and feel myself a little free.

First of all, I'll say very many thanks for the invitation to come to this meeting. It's a major honor for me to stay here, and I have never been in a meeting like this beforehand, because we have heard a lot about FDA, but we have not known how they are working.

I'm a clinician, and my talk will primarily focus on the clinical part of it. What is the problem we are discussing in this? How do we look on that in the clinical part of life? And I heard from some of those questions over here, I probably will answer hopefully some of them, because the clinical part is the problem. How can we handle this very big, what shall I say, thing we want to do?

So it's a clinical thing I'll do. And secondly, I probably am the only one in this room which is not an English speaking as a first language. That may, you have to forgive some of my faults with my language.

I'm a GI surgeon, as you said. I have been what you call a general surgeon. I have worked very much and made a lot of surgery on bowels, but the last 25 years I have been focusing on the problem with the wounds we always make.

The content of my talk really is the burden or wounds in general. I'll give a little general description of what I am, my background from me. It's a little different from this. It's maybe not directly the topic here, but to give you an idea.

The optimum clinical organization, multidisciplinary wound center, and then I go into the barrier wound healing, microbiological factors, treatment on infection, and then the evidence problem, which I have been working very much with: evidence of what in the wound area, evidence problem in the wound area, outcome/endpoints in the wound area, present status, and what can be done.

I hope you will in some way learn a little about what's going on, from my point of view, in the clinical part of it. And now I'm coming from another part of the world, so there may be some news that way around.

The burden of wounds, we all know these wounds. That is the problem. We call them problem wounds. We call them chronic wounds. We have decided in our part of the world, in EWMA, which is the European association for wounds, decided to say non-healing

wounds because you hear so many different word for what's going on. But we call them non-healing wounds.

The burden of chronic wound, in Europe, we published a paper some years ago, 1½ million patients. I'm quite sure that is too little, far too little, but that what we have recognized. Most -- oh, excuse me. It's the most important call for community nursing time. Up to 50% of the inpatient has a wound. Whatever they are for, up to 50% of them. And it's very costly.

The same thing we did -- I was part of an article came same year in wound repair and regeneration for U.S. You say 6.5 million patients here. I don't know anything about it, but I would expect that is far too little, too.

The cost is huge, and the problem is rapidly growing because we have diabetes, aging, obesity. These three things, especially with the diabetes, is exploding worldwide. I have just been in the Middle East now, where in Saudi Arabia and the Emirate, 25% of the population has diabetes in the Emirate. In Denmark, it's 4 or 5%. Twenty-five percent. So it's spreading very much.

The problem in Denmark, we know we have a little more than 1% of the population have a wound for all time, a major problem with a non-healing wound. The expenses of all the healthcare expenses, 2 to 4%, almost 4% is going directly to treat wounds. And that's a good argument when you have to negotiate with the political people.

In Denmark -- only to give you a background for what we are doing in Denmark in the healthcare -- and I know it has been in your presidential campaign now, Denmark has been mentioned for its healthcare. In Denmark, it's totally free for have a scratch or have a heart transplant. You are not paying for anything. It's totally free, all healthcare. The problem is we are paying between 50 to 60% in tax of all we are earning. So it's a bad side and a good side. But I don't think we can continue that, but today, it's totally free.

We have 95% of all hospitals are public. Only 5% is private. And the standard -- I have been living in San Francisco in the '80s. I know how the differences is for your private hospital and the public over here. In Denmark, the quality is exactly the same because it's the same doctors, which in their other time, pastime, they go out and do the same job. The only difference is that the waiting time is different. But the quality is the same. But only 5%. So now you know a little about that.

I'll give you a little, a short description of what I have, where I'm coming from. I have started two wound centers in Denmark: one in Copenhagen '96 and then in Odense at 2003. And these wound centers, the key point with that is they have their own inpatient department. We have 15 inpatient beds only for wounds. We are 53 in Copenhagen working full time with wound, doctors, nurses, whatever it is, and finally paid by the government. We are implemented that way so we have these two wound centers. It's probably the optimal way, from my point of view, to have it. But it's difficult to there, to make.

And the key point for us is we have a lot of good collaboration now. In the beginning, there was not that way, but now we have a very good collaboration with all the department. And I will focus on one thing, microbiology.

Each center has every once a week a conference on the patient who is getting antibiotics. And we make decisions exactly how to take it away and so on because we have realized the problem with antibiotics also, but when I come back to the resistance, the resistance of MRSA in Denmark is still only 1%. And that's because we take very much care of what we are doing with our antibiotics especially.

It's a younger edition of me, and this is a professor of microbiology who was very interested in the wound patient themself. He came, and we have a conference every week about these things.

Then go to, little more specifically, the barriers for healing. The main barriers for healing of non-healing wounds is bacteria, infection, necrotic tissue, exudate. But I will say, this one is the main thing. The curious thing is in the literature, if a wound is totally sterile, it's not healing as well as a small amount of bacteria. It has been shown. I think it's something related to the inflammation reaction, but a total sterile wound is actually, the tensile strength developed is smaller if compared to a small amount of wound, of bacteria. If you have too many bacteria, of course, and you get a clinical infection, then you have a delay.

We know that infection relates to bacterial load, virulence, host resistance, like this one, and I'll go shortly into that.

What we are working with: We are primarily working with the numbers of bacteria, the virulence of the bacteria, and the resistance of the bacteria. Biofilm I will not mention, only with one slide, because I am -- in this meeting, biofilm in some way is a little forgotten. But I'll come back to that.

The number of bacteria is probably -- we know, in acute wound, there is a direct correlation between the increasing numbers and the infection. I don't think a non-healing wound, it's the same problem. The key point is that the numbers of bacteria is not a good measure for whether there will be infection or not. The virulence, from my point of view, is much more important, what we have investigated.

We have this, you know, this one. All wounds are contaminated. Many wounds are colonized, and a few wounds has a clinical infection. These steps is not a new, but unfortunately, from my point of view, clinically looked at, we got a term called "critical colonization." It came about 10, 15 years ago. And clinically, I have to say, I don't know what critical colonization is clinically.

When I'm looking at a patient, I can't say -- I can say, is there a clinical infection, or is

there not. I cannot say whether it's critical colonization. Unfortunately, from my point of view, critical colonization has been an indication for something we should use. But clinically I have to say, I cannot use it.

So we have these steps. And what we are looking at here -- and that's one other thing, the discussion this morning also. If we are looking about antimicrobial in dressings, and it's not working very much, you have to, from my point of view, much more to distinct, is it a clinical infection we are talking about, or is it for prophylaxis?

We never use antimicrobial for prophylaxis because we have no evidence that it's working that way. We use it for clinical infection. And that's a key point. And I think the discussion here has not make that split between these two things.

If we are looking at bacteria, we know that we have three type of bacteria: invasive, local, and opportunistic. This one is the key point for in the wound area. And the real bad one -- the normal tissue, if you have an invasive one, you can put it on the skin, and they actually go in there. It don't need to have an open wound. It can directly go into the tissue itself.

We have two bacteria we are very much afraid of -- some of the other one, too, but still, the two worst one is hemolytic streptococci Group A, C, and G, and *Staph aureus*. The reason we are so afraid, especially of the streptococci, is that it can spread directly in the tissue, like in the erysipelas we have here. You can see, we make marks, and then we know exactly where they're spreading.

Streptococci have produce so strong enzymes that it can directly -- this is the one we actually dissolved our heart attack embolus, this one. And so streptococci can go directly, spreading. That is the worst case we can have, especially in an ischemic leg. Then we are really in problem.

Compare to the staphylococci, the staphylococci has very weaker enzymes, which

meaning that *Staphylococcus* primarily is doing localized infection, like abscesses. Abscesses is not very nice, but they are not as dangerous as the one who can spread directly, the streptococci. That's the reason, in Denmark, if we have -- in sweat we find a streptococci A, C, and G, whatever there is any signs of infection, we give 5 days for penicillin. It's a must. We want to get rid of them in a wound patient. I'm only talking about wound patient.

Then we have to look at about diabetes. What is the real problem with diabetic foot patient? The real problem is the risk of infection. The risk of infection in a diabetic foot patient is four times higher than in normal patient. That is what, where we are afraid, because if they get infected, and you can see like this. This is a patient in 24 hours developed a full infection. I was cutting there, and pus was coming out. And we have to amputate.

And we know, if you have major, have one major amputation, up to 50% of them have a second one in 5 years. And 5 years later, half of them is dead. So a major amputation in diabetic patient is a worst prognostic sign, really bad one.

So that's there where we actually have this. Then we are talking about the resistance also. And the key resistance, I would say, there's a lot of different thing who's to be resistant. But the key problem in the wound area is MRSA and *Pseudomonas*.

Pseudomonas normally is coming when you're used all types of antibiotic on a patient, then you end up with a *Pseudomonas*. Normally, a *Pseudomonas* is not that bad, but in a wound, it can make a lot of problem. Also, if you make split skin, and so on, you -- it will never take, if you have *Pseudomonas* in. So that's the two one we have.

And then I will show -- there we are, this map. It's some years ago, but I think it will still the same. If we are looking where we are standing now, half of the patient, wound patient actually, would have an -- 50% would have a MRSA incidence. In Denmark,

Scandinavia, and Iceland, and Holland, we still have lesser than 1%.

So what we can do is we can isolate our patient. You cannot do it if half of the patient have it. We isolate them and then can give a good treatment that way. But that's because we have been very precautious with what we are giving. We cannot give a -- only a doctor can order giving antibiotic. In Germany, you can buy it in a normal shop without anything.

So that was one of the things you talked about. United Nations just have looked at it now. EU actually saw it some years ago, about 4 or 5 years ago. They already said, the resistant development is a major problem. We need to focus on that. And we had a major conference in Denmark in 2012, and that's what I'll go into.

Only present EWMA, European Wound Management Association. It's an umbrella organization, started in '91, for about 25,000 European professionals from 46 countries. And we have looked upon what we could do with the resistance. And we have some initiative, and I'll go into shortly into a couple of them.

The first one was we make an Antimicrobials and Non-healing Wounds Evidence, Controversies and Suggestions Group. And we published this paper in 2013, and that may be the reason I'm standing here. Otherwise, I can't understand why I was chosen to come here. But it's on 93 pages, and we really go into what we can do with -- come on. Oh.

The objectives of that was produce an update, where are we, in each part of it. What is the evidence on highest level? Show uncovered controversies. For instance, we have what is critical colonization? That, we have discussed, and put whatever conclusion on. This one, if you want to have it down, you can have it for free, to go into the EWMA website. Then you can download it for free. It was published in *Journal of Wound Care* also.

So we want to have perspective for the future work and messages we gave to the

stakeholders, patients, healthcare, political makers, politicians, industry, and hospital administration. And I think, actually, it has been working that way. Slowly, I can see we get more and more feedback about these things.

The focus area in this publication is only local administration, local treatment. We are not focusing on acute wounds. It's non-healing wounds, not on burns, animal models, and systemic antibiotics. Only if we need to have some references, then we use it. Otherwise, it is primarily on local topical treatment.

Then I allow myself only to give two words about what we are doing in Denmark locally. And I know the evidence is only almost zero. It's my opinion. But that's what we are doing. We debride the wound, then clean it, and then we have this discussion. Should we put something on this wound, antimicrobial things, or not?

And first of all, local antibiotic in Denmark is forbidden. You must not put a local antibiotic directly in the wound. Microbiologists have said, no, we don't have it because the advantages compared to the other antimicrobials is not very big. And what you are doing is you are developing resistance.

So that's one thing. We have Gentacoll. I don't know whether you know it. It's gentamicin and collagen. For a few cases, we can use that, and only for 1 to 2 weeks. It's not working, then stop it so you don't develop any resistance.

And then we have discussed a lot of other things. All this is not used in wounds at all in Denmark. We have never used them for many years. We are still using iodine. Unfortunately I have to still mention a product, otherwise I wouldn't do that, but Iodosorb is the one we use because it has some good things, and I'll come back to that.

Then we use silver and other. As you know, we also use honey. And honey and the iodine has never been shown to give, as well as I know, any resistant bacteria. Honey has never been shown to do that.

Only -- my only experience, the way we do it, where I am, when we have a very, what's a infected wound, we use iodine first. I think iodine, from the clinical experience -- I know the evidence level is not very high there, iodine is the most strong of all the antiseptic we have. It has a negative effect, as we know, for the epithelialization and new granulation tissue. We also know that silver has lesser -- from my point of view, it's not as strong as iodine, but it has a better, what's a relationship to the epithelialization and the granulation tissue.

So that what we are doing, we make a debridement, of course. Then the iodine product, we use for 4 to 5 days and then stop it, and go to silver. That's the classical way we use it. And then we use maggot in the final end. I want to say that we have used, we have treated almost a thousand patients with maggot. It's very nice. But I won't -- it's not the topic. But this the way we normally use it locally.

And then another problem, as I said, I have -- during the paper I get from this, from FDA, you have not mentioned biofilm. Whatever we rely, I don't know how much harm biofilm is doing in non-healing wounds. I don't know it exactly. But we need to know what we should do. Is antibiotic or antiseptic locally, are they working on biofilm? I have never seen anything. We need to go into that, too, because otherwise we can't solve it.

We know that the golden standard is debridement. Sharp debridement has a certain, then we take the whole thing away, no biofilm. But in other cases, we don't know whether what we discuss here, local antimicrobials, does it have any effect in biofilm? We need to know that. I think that should be taken up. I haven't seen it as a topic.

Oh, one thing I only -- some literature has shown that iodine is working on biofilm, but silver is not. So it already has been a little about it, but in this meeting, I haven't seen it.

The next thing we have done in EWMA is we have make an antimicrobial

stewardship group also. And could you -- I don't know why this is not working. The program aim is to reduce inappropriate use of antimicrobial as the four earlier speakers were saying. We want to make a publication, and I'll show that in a minute, education, symposia, regional courses, and so on.

The first thing we did, just 2 months ago, this paper is what came out. And it came -- and in *Journal of Antimicrobial Chemotherapy*, and it's actually, from my point of view, a good paper because it gives some guidelines for what to do. I can see, this is the summary of it, and a little too busy slide, but we want to -- the object here is to provide clinicians an understanding of the basic principles of who, how, and why we should do these things.

And we have, as a result, antibiotic therapy is only required for those that are clinically infected. Definitive therapy should be based on the appropriate collected specimens. Prescriptions should be very narrow. AMS teams should be interdisciplinary. There should be some bacteriologists and also these things, but also clinician into it.

So that's what we are, and you can find it in Antimicrobial. It's up now. It's online. It's not printed yet, but it will come there.

Then I will go through the evidence. We all know this Cochrane. You discussed that beforehand. We know 1a is the golden standard, meta-analysis, systemic review, and RCT. I have -- telling this one, because I think we have to focus on them, too, because exactly what we discussed before. Can we -- and I'll come back to that, can we do the correct thing?

And the key point is, which type of intervention technology and dressing material to use and how to do it correctly, based on evidence. That is what we want to do. The problem in -- I don't know how it is in the U.S., but the problem in Europe is now all the governments has learned, if there is not evidence on the highest level, they will not reimburse to the patient anymore for dressings. And that make a major problem for many

of the patient because they can't pay for it. And then, of course, cost effectiveness also.

Evidence problem, as I see it, and I have done a lot of research in this case and made RCTs, sufficient number of patient with standardized wounds is the first thing. Is the patient comparable? So I will show, how can you -- this is venous leg ulcers, how can we actually get 200 patients in each group with the same wound? The same thing for diabetic foot, a granulated one, huge one, with infection, how can we again get that?

What about pressure ulcers? Small, but big one here, terrible one here. This is the hip joint. You can put the finger directly through the hip joint. And also in acute wounds. I have not worked with burns. I have to say that, so that's the reason I am not going to go there. In the wound center, we have a burn unit take care of that also.

But again, it's extremely difficult to put so many people together in a group which is comparable. Another thing is, the other thing was, is the patient comparable in relation to other diseases? We know that two to four times after it becomes 60 to 70 years old, have a wound, or more often has a wound. And that means we get old and fragile people who are suffering from several competing diseases, many of them. That means we may also again have a problem because they are not comparable.

Then what should we say, evidence on what? We can say three things, and I have borrowed this from Patricia Price. Efficacy, healing recurrence, very well known. Efficiency, frequency of visits, day in hospital, among others. And effectiveness, cost and quality of life.

The key point has been -- and FDA, I have to say, until I got a paper now that you have given a little opener on what is the endpoint, but until 2006 or '7, actually the endpoint was full healing. And for a clinician like me, it's a problem for a lot of the patient. And that means a lot of -- for instance, for the diabetic foot patient, DFU, the problem has, we have put into the group, we have put very, very easily healing wounds because they

have to heal in a certain while.

So the wound we really have the problem with has never be investigated, only the very superficial one because it has to be full healing. So that has been, from my point of view, one of the major problems in this area.

Outcome and endpoint in the wound, because we have to focus on endpoint. An outcome is objective/result of an evaluation/study. We can have primary one, which is the focus of the whole study, and we can have secondary one, which is secondary questions. Then we can have clinical one, related to observational outcomes, and surrogate, so on. I won't go in detail with that. You know that much more than I am.

I very early, actually, already back about 8, 10 years ago, say is endpoint/outcomes in the wound area sufficiently developed to be usable in the wound area? And for this reason, we made another publication -- I have all of them here -- in EWMA. It came in 2010. And I think it's the first, still also almost the only one, "Outcomes in Controlled and Comparative Studies on Non-Healing Wounds." It's published in *Journal of Wound Care* there, where we really went into which type of a outcome do we have, which one can we use.

And I will suggest that you should look at it if you are interested. It's very detailed, but I think it's maybe the first one which is going into it. We make a recommendation for medical devices, framework for the clinicians, and healthcare technology. So it should be an information for a lot of involved people.

We made an investigation at that time before we actually published this one, where we looked at which was the endpoint from all trials in 2003 to 2009. We found usable 371. We found thousands of articles, but usable 371, of which 76 was actually usable, the way we want to evaluate outcome. And we found out that healing was 60% of all of it. And that's the reason we are discussing here, healing. But is healing the only outcome?

If we are looking at infection, only 4.5, outcome was only 4.5 of all the published endpoint we actually had. And that says a little, I think, a little trouble, problematic that way. So healing has been in some way reduction of a wound size, or something like that, or full healing has always been the major thing. Maybe we should go other ways.

I will say, what is the evidence when we are evaluating from these things? And no or little evidence, perhaps probably evidence -- I can say already now, from my point of view, there is no evidence on 1a for anything in our area.

No or little evidence, debridement, little evidence for whether we should debride or not. But we know if we have an infected diabetic foot and not debriding, then the amputation, major amputation level will increase with a factor 1.6 for every day we are not doing it. So I think it's not a discussion whether we should, but Cochrane saying there's no evidence for it. And what they say, the only evidence they found was hydrogel dressing increased healing. And I don't know why hydrogel is put into a debridement system, but read it. It's one of the -- what, there is no evidence, but should we not do debridement then?

Other things: Efficacy of modern dressing, only no significant differences in terms of the proportion of healing. Proportion of healing again. Ulcers, reduction of wound sites and so on, no difference. More trials. The same thing with dressings, substantial number of studies, little evidence. We cannot use it for anything. Silver, the same thing. Whatever, we like it or not, silver is not better than gauze, they said, and so on.

And then we are back to what was discussed here. Are we only looking at healing? What about what will the patient? I know I don't want to have gauze into my wound. It dry out in 4 hours, and then it's very painful. So there is other thing we should focus on in this game, not only full healing.

But again, in the Cochrane Review, say no evidence. Evidence which has a more --

we need to have more trials. The same thing, antimicrobials, several studies, little evidence. Again, talking about is it healing or is it infection rate, it's not mentioned. It's only healing mentioned here.

And so, also in Iran and some other places, they use this one. There's no evidence for that, I would expect that.

So perhaps are some evidence are only -- it's not for the topic for this meeting, but we have some evidence for the topical negative pressure. Some evidence for hyperbaric oxygen and rather good evidence for use of compression. So there is a few areas where we have managed to do it. But on 1a, no evidence.

So the general summary of the present status is there is limited evidence on the highest level for technique or devices. The major problem is poor quality of the trials.

What is the consequences? And that's what I want to say. What should I do as a clinician? There's no evidence; should we say, should we not use the dressings? Should we not debride? Should we use it in a few special cases? Or should you use the cheapest? In England, they actually have said you shall choose the cheapest, which is gauze.

Again, is that the best for the patient? Whatever we like or not, but it is a major problem for me because if people say there's no evidence, should we not use it? It is one of the things we have to think about in the clinic.

And following point we also have to focus on, there is insufficient sample size, which means that a Type II error will show a false negative result even if the product is working. The Type II error is probably one of the major problems because all the thing, the trials which is published is on low numbers because it's difficult.

We shall always do the best possible thing to do the trial, but is it a RCT? One thing is a few cases we have had a lot of patient, but then the thing has been used with the wrong indication. And I don't know whether you know, can some of you can remember, with the

VULCAN study, published in *British Journal of Surgery* in 2009, where they found out, they put through six different silver products, dressings without silver and with silver. And they found out the wound was not healing faster. And they say there's no effect of it.

Yes, I could have told them that. The wound was totally without any infection. It was normally healing wound. Silver is not working, from my point of view, on normally working or normally healing wounds. The indication for this is infected wound. And that's, again, what I -- you have to split up there. From my point of view, you cannot improve, not clinically seen, improve the healing in a normal healing wound if you put, for instance, silver on it.

Then, is it unethical to make an RCT for evidence in some of them? Yes, in debridement. I will not be in the control group, at least. And there was some years ago an English professor who made an investigation of another problem, parachutes. There's no evidence that you should use a parachute. He went through the whole literature and didn't find anything, only to say you cannot use RCTs in all cases. There will be these places.

What can be done, then? We can go for new outcomes. It's not only accidentally shown. We need to have new outcomes. Infection, frequency of stay, cost, and so on. We shall always have healing. We shall always have healing as the first goal, but we could go for other one, too. And I think infection would be one of them, which will be very worth it to do.

And that was the reason we made this study, and we made a lot of recommendations for this, and it's only to show that we actually put on a lot of recommendation, what we could do, so I'll not mention them here.

Other important questions to consider in the future. Should we actually have evidence level on different -- should we have different evidence level related to which type of wounds we are treating, which stage of wound healing we are in? Is controlled

nonrandomized study or cohort studies usable? I think they are, because otherwise we will never get evidence in anything.

Should endpoint beside healing be accepted? Yes. Should a consistent reproducible approach to define, evaluate, and measure appropriate, adequate, and clinically relevant outcome be developed? Yes. We need to find out how we can evaluate these things, and we need to agree with that because some people do it one way; you do it one way over here, we do it other ways in Europe.

And for this reason, we finally -- I really advocate for EWMA; we made a study recommendation, a small one here, which is for young doctors, the first time they shall make their RCT, what should they go for to make it optimal? I haven't seen that done before. This for the venous leg ulcers. But we need to do like such things. How can we improve? How can we do better things? And then we have to relate it to the area we are, in this case the wound, and take care of all of the problems we have in the wound, with selection and so on.

So, in conclusion, ladies and gentlemen, this clinical part of it, infection is probably the most critical complication for non-healing wounds. We need a tight collaboration between healthcare providers, microbiologists, administration, and the patient, of course, himself, to avoid development of resistant bacteria.

In the evidence area, we have problems. Important question is wound type, type of trial accepted, endpoint, consistent and reproducible approach to evaluate. Should that be developed? Yes, I think so. Thank you very much.

(Applause.)

DR. HARRIS: I'd like to thank Dr. Gottrup and the FDA presenters for their presentations. Now it's time for additional clarifying questions, if there are some, from the Panel. Please feel free to ask either Dr. Gottrup or FDA at this point.

Dr. Alam.

DR. ALAM: Hi, Dr. Gottrup. Thank you very much for that outstanding and very insightful talk. That was certainly a pleasure to hear from you and to learn so much in a short period of time.

I had a question pertaining to acute wounds. I'm a dermatologist, and we do surgical dermatology, too. We create many thousands of acute wounds a year. And the party line in our field is not to debride so much. We often use occlusive dressings for those acute wounds. And I suspect you would agree with that.

And in addition, sometimes antimicrobials, topical or otherwise, are used to, quote/unquote, "treat inflammation" and expedite wound healing, especially for lower extremity wounds and other wounds like that. Can you talk a little bit about your experience with acute wounds and whether some of these topical products, whether the antimicrobial or not, may be appropriate in the management of such wounds?

DR. GOTTRUP: I allow myself to jump a little. I will only say, because I am not -- the simple acute wounds we don't have in the wound center. I'm a surgeon. I know that from old days, but we don't have the simple one. We have the more problematic one.

But if we're talking, for instance, about venous leg ulcers, a lot of research say debridement. I have seen so many articles saying, then we debrided a venous leg ulcer. You shall not debride a venous leg ulcer. If you have to debride black necrosis away, it's not a venous leg ulcer. It's ischemic ulcer. So it's only a little thing. Debridement is in the venous leg ulcers, and it's more cleaning itself.

And I would again discussion, and it's the same thing with the acute one. Is it infected? The key point for me is I will never use an antimicrobial if it's not infected. That's what I will say. I will not use it prophylactic, put it on, because normally in 24 hours, the first epithelial cell actually had covered if the surgical wound is correctly adapted. Then the

first -- if after 24 hours, that already the first epithelial cells has moved over. So it don't need to have -- you shall not use it for prophylaxis. That my problem with it. You shall use it if there is an infected and -- then what is an infection? Clinical infection.

Whatever we like or not, we need to define and say, as a senior doctor, says if he say there is a clinical infection, then you have to follow that because we can never -- we cannot measure an infection. That's one of the thing I have seen also discussed here. An infection, what is that?

It is from the clinical part -- I'm looking for the clinical part. It is when you are standing over the patient and you have to decide yourself, is it infected or not? At once you cannot put in something and draw out some fluid and see, say, that's a lot of bacteria. There's always bacteria. So it's a clinical point of view. You have to decide whether it's infected or not. If it is infected, then use antibiotic; otherwise, not.

DR. HARRIS: Dr. Hunt.

DR. HUNT: Thank you for those excellent presentations.

I had two questions, one related to the antimicrobial resistance. I clearly understand that's a serious problem worldwide. One of the issues related to our discussion today, though, is how can we really separate out antimicrobial resistance with respect to local wound management from systemic therapies, which I think in most situations, both are going to be utilized in the clinic? And do you really have good data separating just local wound therapies versus a combination of oral or intravenous antibiotics?

And then the second area is sort of a follow-up to the previous question and your discussion about clinical judgment. Much of the discussion today has not been focused on an area that I practice in, which is oncology. And so I have patients who have been treated with radiation therapy and systemic treatments that lower the immune system. And so clinically it does require a tremendous amount of judgment.

If I wait too long to treat a patient with antibiotics, the infection can become so severe so quickly that we may have difficulty getting control and management of it. So it does require that clinical judgment in terms of intervention. And that's something that's very difficult to define and regulate, so --

MR. KITCHEL: Thank you so much for that, that question. I'll do my best to answer and also ask any of my FDA colleagues to feel free to weigh in on the clinical side of things. I'm just a microbiologist, a very humble microbiologist.

So regarding your question about, you know, separating local wound management from systemic therapies, one thing that I was trying to illustrate in my talk was that the reagents that are being used for these two are pretty different and quite distinct.

For the purpose of this Panel meeting, what we're discussing, as far as antimicrobials in wound dressings, these are broad-spectrum reagents that have been previously implemented as disinfectants. And compared to the systemic therapies that we see, as reviewed in drugs, which are targeted, okay, so it takes lower concentrations to use those products to target and try to deal with an infection, whereas when we're talking about the localized management, we're really focused today on just the growth of microbes within these products.

And so just a little distinction that I can add, as far as, you know, there's a difference in types of reagents between those two, and if we can try to separate those, I think it's beneficial.

Regarding the clinical impact, I would defer. And if we don't have a good answer now, I'm sure we can get back to you after the break. But is there anyone who would like to speak on the clinical?

DR. ASHAR: Yeah, this is Binita Ashar. I just, I think we've put in front of you a very challenging question. And I think the talks that you heard this morning were more focused

on the dressing itself and reducing the bioburden on the dressing, which are the devices that we are here to discuss. But we're doing that in light of the entire ecosystem, recognizing that wound care is not isolated to the dressing itself, that even if you go even a step back further, you think about issues related to not only the individual patient but society at large.

And so the challenge for this Panel is to chip away at that and to start thinking about, you know, do we need to recalibrate our thinking with respect to how we regulate these products? And that is going to be the challenge for tomorrow is are there special controls that may be possible to recalibrate things, in light of what's unknown? But there also is some information that's known to ensure that the benefits outweigh the risks and that, you know, that we look at these products for their safety and effectiveness.

So I think you're asking the right question. I don't know that there is an answer. And that's why we're convening today.

DR. HUNT: So I guess the data that was presented with respect effectiveness, you know, is it easy to separate that from just the devices versus how many patients were also receiving some type of systemic therapy at the same time?

DR. ASHAR: We haven't been able to do that. So that is the challenge. There are so many factors that come into play. And what we're focusing on today is just the dressing itself. And when I talk about the dressing or the drug, we're not even separating the drug from the dressing. We're looking at that as one product, together.

DR. KIM: Hi, this is Peter Kim, Division of Anti-Infective Products, CDER.

It's my understanding that the products in this FRO code are specifically for prevention, or they're not specifically for treatment of infection. So I think, once again, we have to separate that out, that when the antimicrobial is in this combination product, it's not for the treatment of the infection but actually as a preservative to keep the dressing

from, I guess, becoming contaminated.

DR. MARQUART: And this is Laura Marquart. The other thing with -- so the data that we presented talked about, you know, with what it looked at -- again, as everyone reiterated, what we're talking about is these agents that are in these dressings. And really, what the data said is for non-infected chronic wounds, just as Dr. Gottrup said, we don't need to use it. It's those ones where we have to use our clinical judgment, and that's where we would put this dressing.

Some of the studies were used in conjunction to -- these were clinically infected wounds. The patients were on systemic antibiotics. And then an antimicrobial dressing was used in conjunction with that. And then others, these were ones that were not clinically infected, but they weren't healing despite optimal wound care. And so an antimicrobial dressing may have been used.

But these dressings are not, again, used to treat infected wounds. They're just help. The main goal of these is to cover and protect, provide a moist environment, and might hopefully decrease the bioburden that's on the dressing itself.

DR. HUNT: Thank you for that great -- oh, sorry.

DR. GOTTRUP: I only have one question for you. You said it's a problem to decide clinically whether it's infected or not. And it has catastrophic, what sort of problems afterwards, if you don't start treated the right place. How do you decide it yourself in the department?

DR. HUNT: I think it depends on the underlying factors related to the patient, you know, what sort of treatments they've had and what other risk factors they have with respect to obesity, diabetes, previous treatments that lower their immune system, and what their current hematologic profile is. So all of those factors come into play, and it's always a multi-disciplinary decision. It's not just one person. But the point is that I think

clinical judgment does come into play.

And I guess, with respect to my other questions, I wasn't really making a point as much about the prevention of infection but the discussion about are these devices maybe contributing to antimicrobial resistance? And so that's where I was trying to get more information about the data, because most of the time, these patients, I would say, are often going to be getting these local things and systemic agents. And so how do we know that one is contributing more than the other? Is there data saying that chronic use or even just short-term use of these is going to lead to significant antimicrobial resistance?

DR. GOTTRUP: Only, before you answer, that's exactly what I'm saying. You make a decision based on how the patient are, the clinical signs, and I don't think we can get it better. So you're doing the -- for what I would say, the key point is that you have focus on it, if you're not forgetting it. You have to make a decision, as you said, with all the influencing factors. And that's a thing we shall always do, but it's a clinical decision we are making to find out. We cannot measure it.

MR. KITCHEL: Thank you for that clarity. Just really quick, to try to address that clarified point, I think we've learned an awful lot about antimicrobial resistance as it pertains to our systemic therapeutics. There has been higher scrutiny with type of a resistance as when we're talking about antimicrobial failure, we're ultimately talking about infections, impact on a patient level.

And so I know at the CDC, directly, they're doing research on antimicrobial resistance mechanisms, and there's a lot that has been learned over the past few decades specifically pertaining to those therapeutic drugs.

Regarding the contribution to antimicrobial resistance in the products here today, which is the clarified point that you brought up, it's a great question. And really, that's part of the purpose that we're here, and we're looking for your insights. We do know that it has

potential to contribute to antimicrobial resistance. We do know it's indirect, as I talked in my presentation. Knowing about specifically co-resistance to antibiotics is a concern, and plasmid-mediated resistance is a concern as it more rapidly contributes to the, you know, to spread of this resistance. But as far as the prevalence, you know, there's a lot of question marks still there. I think a lot of research is still needed to be done on contributing factors of antimicrobial resistance, specifically with the reagents in these wound dressings. Thank you.

DR. SOOD: Thank you for that wonderful talk. As Dr. Gottrup pointed out, it can be very difficult to figure out if a wound is infected and what the critical concentrations of bacteria are or if there is specific groupings of bacteria that make it more likely for it to be infected or not.

So I'm a little bit confused about the antibiotic resistance in this situation because we, as an infectious disease doctor, one of the endpoints that we look for is to use topical treatment in order to prevent systemic antibiotic treatment. And that should actually, in theory, have less resistance because it's localized and you're getting higher concentrations at that site and you're not impacting the GI biome, etc., etc.

I became a little bit confused about this idea of we're only thinking about the antibiotics in this scenario as prophylactic, and they're not really being used for treatment. Can you clarify that a little bit, if you don't mind?

DR. GOTTRUP: If you -- if it's me you want to answer, I can say the way we are doing it is that if we find a local infection, we start to use a local antimicrobials. And not antibiotic, as I said. And if it's spreading in spite of that, then we start systemically but not before that. At the local thing, we continue locally only. If it shows spreading, then we start systemic.

DR. KIM: Hi. I think we need to clarify, and so I'm from the Center for Drugs. And

my understanding is that the way these combination products are labeled, they're not labeled for treating infections. These products are specifically labeled such that it's protecting the wound. And I'll let my colleague --

DR. MARQUART: Right. So in terms of these products, we're not talking about topical mupirocin or topical bacitracin. Or gentamicin. These are the wound dressings with chlorhexidine, with silver. Those are what we're looking at, at this Panel.

DR. KIM: But I think the questions are key. This is key to the whole issue because there is confusion among everyone as to what the actual indication is for these combination products and whether or not these combination products have actually been studied in any way for the treatment or prevention of infection.

My understanding, though -- and once again, I'm from Center for Drugs -- is that these combination products are specifically labeled for protection of the wound. And so the antimicrobial agent inside of that dressing is specifically to protect the dressing or prevent contamination of the dressing.

DR. MARQUART: Okay.

DR. KIM: That's my understanding, and anyone from CDRH that wants to --

DR. MARQUART: Yeah.

DR. HUNT: So if we could get some clarity on that, that would be great, because clinically we -- I would use them in the same way that I would use topical antimicrobials, which would be to "treat," quote/unquote, local infection.

DR. ASHAR: Right. I can --

DR. HARRIS: Okay.

DR. ASHAR: I can clarify. This is Binita Ashar, CDRH. What we're looking at today are wound dressings which consist of solid dressings or ointments and creams or wound washes that contain these antimicrobials. They are not regulated as drugs. They are

regulated as devices that include these chemicals in them.

We're looking at these products for their action on the dressing. And by dressing, I mean all of those three categories. So we're not looking at their interaction with the wound, although the reduction in bioburden on the dressing itself may have clinical implications.

And so I want to make sure that I -- I think this is a great discussion, and these are actually the questions we want you to focus on. And actually, you can see in the Panel pack on Questions 2 and 3, they are precisely these types of questions that we want you to discuss. In fact, Question 2 talks about potential niche populations that we might need to think of differently, you know, patients with infected wounds versus not infected wounds, healing wounds versus non-healing wounds. So if there's other niche populations, we're looking for your feedback there.

And then on Question 3, it's precisely, I think, what Dr. Hunt was talking about. And that is the benefit versus the risk. And here, the benefits of having a reduced bioburden on the dressing versus other risks, including risks of potentially causing pressure to -- in systemic therapies perhaps, to change the decisions that you might have there in resistance issues with respect to the patient and society at large.

So these are precisely the questions we want you to discuss. And so I'm happy that you're starting to do that now.

DR. HARRIS: Okay. It's 12:02. We're going to break for lunch. Those of you who have questions, you'll have a chance to ask those questions as we deliberate later on this afternoon. I'd like to remind everyone to please not discuss the nature of our discussions with anyone or amongst yourselves. And please take any personal belongings from the room. You will not be allowed back in the room until we reconvene at 1 o'clock, and I ask that you be back on time in order to do so. Thank you.

(Whereupon, at 12:02 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:01 p.m.)

DR. HARRIS: At this point, we are now going to proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.
Ms. Washington will now read the Open Public Hearing disclosure process statement.

MS. WASHINGTON: Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting today. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. HARRIS: Thank you. For the record, we have received 11 requests to speak for today's meeting. We ask that each of the public speakers speak clearly so as to allow our transcriptionist to provide an accurate transcription of the proceedings of the meeting. After the introduction of each speaker, the allotted time will be announced. The Panel appreciates that each speaker remains cognizant of their speaking time. Our first speaker this afternoon will be Eric Lullove, West Boca Center for Wound Healing.

I hope I didn't butcher your name too badly.

DR. LULLOVE: It's okay. Everybody does.

Good afternoon, everybody. Distinguished Panel members, thank you for the time. Again, my name is Dr. Eric Lullove. I'm a podiatrist by trade. I am the Medical Director at the West Boca Center for Wound Healing in Boca Raton, Florida.

These are my disclosures. I am here representing the Association for Advancement of Wound Care, 2,500 members, and our mission is to advance the care of people who are at risk who have wounds. And we set the standard for and advocate for all of wound care.

So when we're talking about these patients -- and there was a lot of talk this morning, and I wanted to thank the Panel for a lot of their questions during the earlier sessions because it gleaned a lot of light on what we were talking about, but these patients are extensively complex, okay. These patients have compliance issues, they're diabetic; all these products in this category help us do our job when we are taking care of these people.

And these people are mothers, daughters, fathers, brothers, sisters, family members, grandparents, okay. And I know there was something earlier today, we talked about the possibility of surgical wounds and acute surgical wounds. Well, in an average healthy patient, that would take about 30 days to heal, but when we're dealing with arterial patients and ischemic wound patients, those can take up to a full year or longer.

These are some common causes of chronic, non-healing wounds, and all of these are literally affected by our clinical photos and what we see every day in the field at a community medicine or academic level basis. These are what we see.

The compromise of these patients are extensively complex, and it requires the use of advanced dressings to get our job done. The classic example, which has been discussed numerous times, has been a diabetic foot ulceration. But we also see atypical wounds, venous leg ulcers, complex wounds. Not all these wounds fit into a silo. We can have a

diabetic patient who's got venous disease. We can have a venous patient who's got mixed disease. So these patients are complex, and they're not easy.

Again, clinical decision making revolves around debridement, irrigation, bioburden management. Okay. Sorry.

Wound healing is complex. We deal with biofilm, bioburden, exudate, pain. All of these things are reported to us, and we have to address them clinically.

One of the issues that I want to bring up is the guideline issues. Now, again, the guidelines are guidelines. They're not -- it's not legal ramifications. They don't all agree, okay. In the ABA, and that was discussed earlier, but it was only for partial thickness burns, and they were all respective to don't treat them with antibiotics if they're not infected.

Again, with the Wound Healing Society, this was the 2006 Chronic Wound document. The Panel was not given the Wound Healing Society's 2012 guidelines, which we will provide in the written response for you. Additionally, the American Venous Forum, the Society for Vascular Surgery 2014 Venous Ulcer Guideline was not provided to the Panel.

The American Society of Plastic Surgery again say that rational antibiotic use was based on clinician input and clinician decisions, okay. The ISDA was mixed. It said, "Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy." But at the same time, they said every diabetic foot patient should be treated as clinically infected. There's a issue with the guideline where it does contradict itself.

And again, the Panel was not given the Association for Advancement of Wound Care's 2010 Pressure Ulcer/Venous Ulcer Guideline, which has Level A evidence, which basically stated that we initiate these products on clean ulcers with delayed healing despite 2 to 4 weeks of optimal care, and then we reevaluate the patient every 2 weeks and then discontinue those, these advanced products when the wound starts to progress. And again, we'll provide these documents for you in the written responses.

And again, you can see here, this is the Level A evidence that is in our guideline. The Wound Healing Society -- again, this was all in the summary, but topical antimicrobial dressings may be beneficial in the management of chronically heavily colonized wounds which can decrease the bacterial load and help wound healing.

The ultimate judgment and review from the ASPS says the ultimate judgment regarding the care of a particular patient must be made by the physician in light of all circumstances.

Again, in the guidelines, the expert opinion from the International Working Group on Diabetic Foot Ulcers stated that treat clinically evident infection, and there is no reason to prescribe systemic antibiotic therapy for an uninfected foot wound. And I want to make sure there's a delineation that we discussed, that there is a difference between topical and systemic antibiotics.

And, in conclusion, all the current products are currently covered under the Class II 510(k) process, and I urge the Committee to keep these products in that class. Thank you very much.

DR. HARRIS: Thank you. Our next speaker will be Denis Watson.

MR. WATSON: (Untranslated). Yes, I walk upside down, and I'm from New Zealand, (untranslated). And English is not my first language.

Having got that out of my system, Manuka -- I'd like to first of all, in terms of conflict of interest, I own this company, and we have products in the U.S. market, obviously, with honey. I make no apologies for saying we are leaders in honey science. We have 14 Ph.D.s in our research team. We had a honey research center at the university. And we have now come out of that, and we have created our own honey research team.

One of the things that I'd like to address is keeping honey in the category that it's in, which is Class II, and I want to do a little bit of education, very quickly, on honey.

First of all, we have cleared devices in your market here, 510(k) cleared. They have been 6 years in use. There have been no adverse effects with honey, so I'd like to talk briefly about safety.

Obviously, with silver, honey has been around for ancient times; Egyptians, Greeks, Medes, Persians, Aristotle, all sorts of people have used honey. What I'd like to talk about is medical grade honey and its modern use, primarily because efficacy is a major issue for us. If you don't have repeatability in the honey that you're using, then you're going to have issues.

So we have taken -- over a number of years, in fact, two decades, we have been defining and quantifying honey so that it's a repeatable product in the dressing, that it works every time. One of the areas that we're looking at is all honeys are activated by hydrogen peroxide, which you'd be aware of as an antiseptic. However, Manuka honey does not have a hydrogen peroxide activity. It doesn't come from the bee or the enzyme glucose oxidase. It actually comes from the floral source, which is what makes it unique. And we quantify it for several of those bioactives. Methylglyoxal is one of them.

One of the areas that we're looking at, of course, which I'm sure the Commissioner over here has referred to, multidrug-resistant pathogens, not only in your country but globally. And the cool thing about it is another one of your presenters here from Denmark made the comment that honey has not got resistance to it, no development of resistance to it.

And these are some bugs we've taken out of your labs here and just given them a quick test. They're all multidrug-resistant pathogens. And you can see, taking 10^6 inoculation, we're getting 10^5, 10^6, 10^7 reduction, I guess, in terms of kill rates and also when you look at kill zone. So the honey is extremely effective in taking out these pathogens that are resistant to current regimes and certainly to penicillin.

Now, just a quick for you clinical: I know you guys want RCTs, and there's been some comment about that. Here's a 60-patient study showing reduction in bioburden and reduction in biofilms, 100% heal-out in 12 weeks, from chronic wounds that were not healing over a 6-month period.

Again, diabetic foot ulcer, so we're not going to do those. I'm going to look at mechanisms of action because you've only given me 5 minutes.

Mechanisms of action, we've done gene expression studies and looked specifically at how some of these bioactive fractions are working. There are three areas that are really keen to it. So if you take an opportunistic bug like *Pseudomonas*, and it functions primarily in quorum sensing, so it's very efficient in forming biofilms. It also is very efficient in colonizing and showing virulence.

One of the areas that I'm just demonstrating here, that the honey directly affects the ability for quorum sensing, so it stops them talking to each other. These are three gene expression studies, and there's also a reduction in virulence when you put the honey against those pathogens.

I could go on, but you've given me 5 minutes. There's a simple demonstration there about how the cell wall, in dividing of those pathogens, is inhibited.

All right, what's going on here? There we are. So the absence of resistance is really important for honey in a wound dressing when you're looking at clinical cases now where you've got multidrug resistance. And there's some publications there showing the resistance. No resistance has been developed to medical grade Manuka honey. And repeated exposure of bacteria to sublethal concentrations of Manuka honey in resistant training experiments, the species failed to select bacterial mutants with permanent genotype changes. So the honey is extremely effective in that area.

So my conclusion is pretty simple. One, the antimicrobial efficacy of medical grade

honey is well established. It increases the resources available to clinicians, who are being challenged by these pathogens. The absence of resistance to medical grade honey is clearly a benefit to clinicians and the healthcare system burdened with increasing infection rates.

My, I guess, plea to the FDA or challenge to the FDA is that they should continue to regulate wound care dressings with medical honey as Class II devices because there's no safety or efficacy issues to support changing the risk, changing that, and the risk/benefit assessment of the device is very clear.

I hope I got that done in my 5 minutes. Thank you.

DR. HARRIS: Thank you.

Our next speaker is Joan Siegel.

MS. SIEGEL: Hi. My name is Joan Siegel, and I'd really like to thank you all for inviting me here today to talk. It's a real honor. Since -- wait, here we go.

Since before 1976, since about 1860, my family has been selling this wound care ointment, which is a pine-based ointment which hasn't really been discussed today, for these indications, basically wounds, cuts, lacerations, and burns. And I am the President and CEO of Puremedy. And we are not currently selling to the wound care market, so that's my financial disclosure, but we're selling to health food stores, like Whole Foods and Vitamin Shoppe.

So today's goals, I would really like to advocate for the Original Healing Salve to be designated as a Class II medical device. We are currently under review. And now I understand why that delay has happened, so maybe I'll state my case here. I'm going to show safety and efficacy, minimal to negligible public health risk, evidence for indications for use, and antibacterial effectiveness.

Speaking of, we have here the Original Healing Salve in a typical time-kill study, approximately 90% 1 log reduction within the first 1 minute, 4 log reductions within 4

hours, all tested microorganisms killed within 4 hours, including MRSA, including *Staphylococcus aureus,* including *E. coli, Enterobacter, Klebsiella, Pseudomonas, Streptococcus, Candida*, and a mold.

Also, the salve has proven bacteriostatic. Bacteria cannot grow in the presence of the salve, very important for wound care.

What I want to say is that the microbiologist who conducted these studies for us -- and we have many more -- theorizes, and I'd love to prove this, that it cannot create resistance because he thinks that it is just trapping the microbes in a water-free, air-free environment and inhibiting their ability to communicate with each other and to replicate, so just making them nonviable.

This is another study that actually shows that applying the Puremedy Original Healing Salve topically increases oxygen levels up to four layers deep as well as blood circulation up to 13% in just the first 30 minutes.

Autolytic debridement, of course, very important for wound care, which is something that's been talked about quite a bit. Three ccs of salve were applied on an embedded splinter. The next morning, when the band-aid was removed, the splinter is already on the band-aid. Again, the typical treatment cycle for one application is 6 to 8 hours.

The mechanisms, which we have shown, as well as the observed mechanisms from several doctors at Advantage Wound Care, who have been using this in a testing capacity in El Segundo, but again, the hypothesized method of action is what I really want to talk about, that we really do believe that the viscosity of the tree extracts, the microbial environment, is what appears to be interfering with the communication and the viability of the bacteria so that it's not creating resistance.

A case study, Dudley the cow: Dudley had a severed foot and was rescued by the

Gentle Barn, and now he successfully wears a prosthetic, thanks to our salve. Here we have -- so Dudley's leg was amputated below the knee, and they made a prosthetic, but he was too heavy for his prosthetic. He had some severe wounds, you can see here, from that prosthetic. After 5 days of using the salve, the wounds are resolved, and the tissue looks strong and healthy. After 10 days, remarkably, you can see that there is new hair growing back on that brand new, what appears to be fully functioning new skin.

Here's just a really nice progression of how the Original Healing Salve typically progresses in a wound care. The wound closes from the outside in and from the bottom up. And again, there's some new hair growing back here.

This is me. Don't ever break up a dogfight. I did. These were two wounds down to the bone, and today I do have a tiny, tiny white line where there should be a very obvious scar.

In conclusion, I would like to ask for Class II designation for the salve. Over 1 million users over the past 150 years -- this should say, actually, no serious adverse events reported, pardon me. There have been minimal reports of rash and some topical allergies, and that's really about it.

Every ingredient is food grade, like honey, and generally regarded as safe and effective. Puremedy's Original Healing Salve provides antibacterial action -- I should say antimicrobial, a moist wound healing environment, autolytic debridement, increased circulation and oxygen, protection for the wound bed, anti-inflammatory action because of the increased blood circulation, resolution of chronic wounds in many case studies, antimicrobial power that should not contribute to the formation of superbugs.

Thank you very much.

DR. HARRIS: Thank you.

Our next speaker is Marcia Nusgart.

MS. NUSGART: Good afternoon. I'm Marcia Nusgart. I'm the Executive Director of the Alliance of Wound Care Stakeholders. And who's the Alliance? Well, we're a nonprofit, multidisciplinary trade association of physician specialty societies and clinical associations whose members treat patients with wounds. And the mission of the Alliance is to provide quality care and access to wound care products and services for people with wounds.

Here's a list of the various clinical associations that are members. So the key point from this slide is to show you that wound care is multidisciplinary. There's a whole wide range of healthcare professionals who treat patients with wounds.

The foundations of the Alliance work plan is multifold. We address wound care quality measures. We've created them. We actually have written papers on wound care research. The majority of our time is working with the regulatory associations such as the Food and Drug Administration.

One of the things we did last year, many of you were in the room with us when we were talking to the FDA staff about helping to update the 2006 Guidance for Industry and developing the products for treatment. Last week, we were at the meeting and testified on regulation of human cell tissue products. And we've also worked with the FDA on home care issues.

In addition, so much of our time is spent, obviously, on coverage, coding, and payment issues, working with the Centers for Medicare and Medicaid Services as well as their contractors in addressing many of the reimbursement issues that do face the wound care industry.

What's interesting is that the Alliance has taken this topic very seriously. When we first heard about this in July, we immediately asked our clinicians associations as well as the manufacturers to participate in a series of conference calls and meetings to be able to address our comments today as well as our written comments that many of you have

already received.

Many volunteered on their own to be able to come here today, since they believe it was important for the Panel to hear how do clinicians actually manage wound care patients, about the science of biofilm and antimicrobial resistance, trial design endpoints, and registry.

So the key point that we want to say here is that products in the FRO category should be classified by the FDA in either Class I or Class II, most remaining subject to the 510(k)s, recognizing wound dressing with drugs are used for the management, the management, not the treatment of wounds. And wound dressings with drugs have significant levels of clinical experience including clinical trial and literature in peer-reviewed journals, including safe and effective use. And we'll be submitting many of these studies in our written comments.

The products in the FRO category, that we had mentioned before, is the reason, the rationale for leaving them in or having them in a Class I or Class II, is because they are a low to moderate risk. They've been in the marketplace for many years with a long history of safe and effective use.

And we're very pleased that the FDA is in agreement with us because we heard this morning how the FDA might want to separate them out. I actually looked at all of these products that were in this particular category, and said, oh my goodness, there's such a wide and disparate types of products. And we're glad to hear that you're in agreement with us that you might want to be able to separate them out.

Also, manufacturers do use bench tests and animal studies to establish that these products are safe and effective as those already in the marketplace, and those are, we believe, are effective controls at this point in time.

Terminology. We've all heard this morning three different terms: antimicrobials,

antibiotics, and antiseptics. We believed it was important to define them so that the definitions that are on this particular slide, which are actually from the FDA itself -- they were from documents on its website, with antibiotics and antiseptics being subsets of antimicrobial agents. We recognize that resistance to needed antibiotics is an important issue. But we would like to remind the Panel that the antibiotics of importance are not used in these particular FRO products.

The Alliance was founded roughly about 15 years ago to have a collective voice for wound care. And what impressed me the most -- and you'll hear from many clinicians in the next few minutes -- that the passion, the hard work the wound care community has for its patients. Clinicians want best for their patients, and manufacturers develop products where patients are their focus.

And in terms of wound care is complicated, you've already heard from Dr. Lullove about this. You'll hear from Dot Weir about it. You've already received our comments. We're going to be submitting additional ones after this meeting. We intend to stay engaged with the FDA on this process. We appreciate the opportunity to be able to speak with you today.

Thank you so much.

DR. HARRIS: Thank you.

Our next speaker is Gregory Schultz.

DR. SCHULTZ: Good afternoon, everyone. I'm Greg Schultz. I'm a Research Foundation Professor at the University of Florida and Director of the Institute for Wound Research. Briefly biosketching, I'm a biochemist cross-trained in cell biology. I've been funded continuously by the NIH for 30 years. I'm also President of the Wound Healing Society and served a term on the National Pressure Ulcer Advisory Panel. I serve as a consultant for numerous drug and medical device companies.

My goal, in the next few minutes, is to emphasize for you the key role that infection and inflammation plays in blocking wounds from healing. And certainly, for this group, I don't need to remind you that normal phases of wound healing proceeds through hemostasis, inflammation, repair, and remodeling. But what I will emphasize is that in almost every study that we have done, and along with our colleagues around the world, we've come to determine that a major molecular problem is that these acute wounds get stuck in a chronic inflammatory phase, and that inflammatory phase elevates proteases and reactive oxygen species that are things that actually damage the proteins that are essential for healing and stop the wound from progressing.

So my clinical colleagues' challenge is to recognize when wounds are stuck in this inflammatory phase and to implement the appropriate clinical treatments, including many of the dressings that you've heard about, to change that molecular environment out of a pro-inflammatory status into a pro-healing status.

So what happened in these wounds? These all started as an acute wound. And what my lab and multiple other labs around the world now have been able to put together over the years is that these all share a common molecular status in which there are repeated injuries of ischemia, pressure, etc., and eventually a bioburden develops. Now, that's both planktonic bacteria that Brandon talked about today, also biofilms that we haven't talked too much about, but my colleague from Denmark, Finn Gottrup, has indicated that biofilms are increasingly recognized to play a critical role. In fact, I tease Finn by saying critical colonization is actually when there is a biofilm present in the wound.

Both the bioburden of planktonic and biofilm bacteria increase pro-inflammatory cytokines. We've measured this. They lead to imbalances in the proteases. And these proteases have off-target effects, from a biochemistry speak. And they basically degrade the growth factors and the receptors and the functional matrix that are required for the

wounds to heal. And that results in what you see clinically as a stalled wound that converts from an acute wound into a chronic wound.

The role of biofilms is being more and more appreciated. And basically, from the pioneering work of Bill Costerton, we know that most of the time our innate immune system and our adaptive immune systems are able to deal with the planktonic bacteria. That's why we don't get infected wounds every time we have an injury. But if those planktonic bacteria are able to attach, quorum sense convert from a phenotypic planktonic into a biofilm phenotype, they will secrete the exopolymeric matrix that provides tremendous tolerance.

This is not resistance. This is tolerance. Because if we disperse these biofilms back into single cells, they are still killed by the things that will kill the planktonic bacteria. This is a phenotypic effect, so it is a tolerance that develops. But what does happen is our immune system, particularly our neutrophils, recognize the components of that exopolymeric matrix, and they are incredibly inflammatory. And so these neutrophils and macrophages secrete the proteases in reactive oxygen species.

When we measure the level of proteases in acute wounds or chronic wounds, we can predict which wounds are going to take very long times to heal compared to those that will heal very well, whether they're receiving vehicles or they're receiving, in these studies, recombinant growth factors.

So it turns out our best biomarker that we have been able to identify for what will predict when a wound is going to heal is the level of protease activities in the wound fluid. That is a direct result of the inflammation and infection. Therefore, one of the keys that has led us to incorporate this into teaching information is to talk about the concept of wound bed preparation and the acronym of TIME that captures four key components.

The tissue debridement, we heard the importance of that today. The

infection/inflammation, which is particularly where many of these dressings have an impact, as well as moisture balance, and edge.

Wound bed preparation has become the standard worldwide education for training new wound care providers, so they are inherently interested in understanding how to control the infection/inflammation. We can show that when you debride the wound, if you do not use an effective bacterial barrier dressing, within 3 days, those patients will reconstitute the same amount of bacterial biofilm they had before debridement.

So, in summary, what I hope I've done is emphasize for you that one of the key components that needs to be addressed in wound bed preparation is infection/inflammation. Part of that is using the appropriate dressing. Thank you.

DR. HARRIS: Thank you.

Our next speaker is Dorothy Weir.

MS. WEIR: Good afternoon. And it's a true honor to be here. My name is Dot Weir, and I am a Certified Wound Nurse from the Orlando, Florida area. I work outpatient in two wound centers in that area.

As far as disclosures, I am on several boards. I do speaking as well as advisory board for Smith & Nephew, who did include me in their room block today for this meeting, Hollister and Medline.

So I've been a nurse for a long time, 40 years, and 36 of that has been in wound care. Seventy percent of my time now is spent in teaching, and bioburden is a particular interest of mine in the things that I teach as well as what I write about.

So my key points for today -- I'll get to all these, but the main thing is I wanted you to hear from me, as a practicing nurse, where antimicrobial dressings fit in as a critical piece to our practice.

So coming from many years in wound care, I came from the time where we've

evolved from just thinking about what we're looking at or putting into the wound to what the end result is going to be in terms of the pathway towards healing. And so from coming from a time when we dumped a lot of antiseptics such as povidone-iodine straight into the wound, and have learned since then about toxicity and how to treat a wound better so it's not such a -- since it's such a fragile environment.

I came from a time when we cultured everything. And so early in the '70s and '80s, that's probably what led to a lot of the antimicrobial resistance, or antibiotic resistance that we have today. But we know that wounds are dynamic. They change constantly. And so we have to change our treatment plan along the way to adjust to what we're seeing clinically.

So as Dr. Lullove already alluded to, these patients are very complex. The pathway towards closing a wound is never straight. And so, as I mentioned, we have to adjust that. But we have patients with compromised immune systems. They are out of balance. Their wound environment is out of balance, as mentioned by Dr. Schultz. And so while we can get them to close, so many of them will recur, as much as 80%.

And these patients are in all sites of care. They're at home, they're in long-term care, they're in hospitals. And some of the environments we can control, many we can't. And so the contamination potential is high, regardless of the site.

So I have this in here just to look at. You know, as we look at wound infection as a continuum, we know, as Dr. Gottrup told us this morning, that colonization and contamination is usually something that someone's immune system can work with. And there's no real indication at that point in time for any kind of antimicrobial.

What I want to focus on is, well, he did make a point about critical colonization. And this, to me, is where we have an opportunity. This, to me, is that -- and there -- it's hard conceptually because there's no numbers that we can put to it. It's an assessment. And I'll

get into what we look for in just a moment. But this is where, if we can intervene with the management of the exudate to reduce the bioburden into dressing, then we are probably going to be effective in lowering it on the wound surface. And then, of course, what we're trying to prevent is that bioburden building up to a point where it invades into deeper tissue again, where we would use systemic antibiotics but also topicals.

So the term "critical colonization," I just want you to hear how I look at it, and how those I work with, and how we put it into our practice. It's where we have bacteria on the wound, and now the healing has been compromised in some way. It's thought to be these bacteria are now competing with the wound cells for nutrition, for oxygen. And so it results in the production of toxins. It results in the production of inflammatory mediators that then kick-start that wound or reignite that inflammatory process.

So if we want to call it critical colonization or localized infection, it's whatever our comfort level is, but it's something that we can see. So what will we see? We might see a wound that was granulating before, and now it stops. We might see a wound that the granulation tissue may be deeper red, superimposed on top of lighter red. There may be some pain associated that the patient lets us know about. There may be an odor, or maybe not. We usually will see higher levels of exudate. And so those are the things that we're trying to manage to.

So I was interested in your Question Number 2. That speaks loudly to me because this is what I do. And so when we look at the patients that are going to heal, we -- oh, so sorry. We're going to maintain that environment. If it's healing just fine, we're going to maintain that environment. If it's not healing, we've got to step back and decide what is causing this wound? What are the barriers to healing? And it may be critical colonization. It may be a hostile environment. But we need to have tools to be able to address that. And then, if appropriate, we do an assessment-driven culture, appropriate culture that then

could lead us to appropriate antimicrobial or antibiotic use.

If it's infected, clearly they're going to need systemic management. We will then couple that often with the antimicrobial dressings. If it's not infected, then we have to decide, again, based on our assessment. And from the acute versus chronic standpoint, well, again, the decision drivers are pretty much going to be the same. It depends on the causation of the wound.

So a couple of quick cases: So this is a patient. You can see the outcome. When we took off the dressing, the body's responding in some way. Once we got him all cleaned up, it really wasn't infected. That's at a point when we would use an antimicrobial dressing to try to absorb that exudate better than it was before, as well as manage that bioburden in the exudate.

This is a fellow who was 20 days postop from a skin graft. And what we did was we cleaned him with an antimicrobial. We used a 7-day silver dressing, but we didn't leave it on for 7 days. We absorbed it into a secondary dressing. And 3 days of dressings, 2 days of antibiotics, the wound was this improved. And he actually saved the graft.

So my recommendation is that I'm hoping that the antimicrobial dressings stay in a Class I or II because I would like you to understand that bacteria is a much bigger threat than many of the dressings that we use.

Thank you so much.

DR. HARRIS: Thank you.

Our next speaker is Randall Wolcott.

DR. WOLCOTT: Thank you. I have no disclosures to speak of.

So I was asked by the Panel to come in and talk, a clinical context on antimicrobial uses in wound care. And yesterday, my PA and I saw almost a hundred patients. And today I want to share that patient experience with you, and I just want to advocate for those

patients. I have no other dog in this fight.

So I had the honor to work with Bill Costerton before he died, and it's from that perspective that we'd like to make these four points: First, bacteria matter in chronic wounds; they're very important in chronic wounds, and we'll try to work on what Greg showed us earlier. And then, wound care is very successful; we can't forget that. And in a large part, we're successful because we use antimicrobial dressings. And because we use those dressings, we're able to talk to some of their complications.

So, first, chronic wounds are chronic infections. This is from the European infectious disease society, the brightest and the best across the Continent. And what they say in their guidelines is that biofilms cause chronic infections. Now, that's a game changer, and you got to let that sink in a little bit.

Later on in their document, what they say is, is that chronic wounds are their model for chronic infections, and that's even a bigger thing for us. So basically what they're saying is that the bacteria, the wound microbiota, the biofilm on that wound is a cause for the non-healing of wounds. And it's because we know that information, it's because we act on that information that we have these kind of good results in wound care.

So this is a patient with gas gangrene. And he's got a polymicrobial infection, and it's biofilm. And this is an amputation anywhere in the world. But the problem is the patient refused amputation. Okay. So we're in the clinic, and we're going to do 8 weeks of systemic antibiotics, mainly daptomycin, and we're going to do local wound care with aggressive debridement. And then we're going to de-escalate down to using antimicrobial products for 16 weeks. And he's going to heal his wound. He's going to save his leg. And he has that leg today. It's 10 years later.

So we're not saying that the antimicrobial products treated that wound biofilm. No. They treated a problem that we have, and that's illustrated here with this work from

Dr. Tachi out of Japan. And what he shows is if biofilm forms in the dressings, the wounds don't heal. So it's imperative that we not allow biofilm to form in those dressings, and antimicrobial products can do that. Okay.

Well, then you say, well, if we just indiscriminately start using the antimicrobial products to protect every dressing, then aren't we going to drive resistance? Well, the short answer is probably not. We use silver as an example, and that can be generalized out across other antimicrobial agents. But what we see is that silver has four independent mechanisms by which it can kill bacteria. So that bacteria, in a planktonic state, can become somewhat tolerant, but antibiotics have a single target, and they can have true resistance.

So Greg and I, we're not playing these word games of tolerance and resistance. I mean, these are real things. So resistance is associated with antibiotics, and we know that's a huge public health issue. You know, Brandon talked about the mobile genetic elements that go out across; this is a plasmid, the *mecA* cassette for MRSA. And it's broadcast out through horizontal gene transfer. It goes broadly across the community, and it stays persistent within the community.

Now, that's antibiotic resistance. But for antimicrobials in dressings, we're talking about tolerance to biofilm, apples and oranges. We're talking -- you know, we don't want to group those things together. So I'm with the authors up there that resistance in antimicrobials is really overstated and is pretty much pretty rare.

So let me leave you with this last thought. Okay. These are patients that were told that they had to have their legs amputated because of their wounds. If we treat them in a clinical setting where we have antimicrobial dressings, they heal those wounds, and they don't lose those legs. And we use less antibiotics. But if we treat them in a hospital or in a nursing home where we don't have antimicrobial dressings, it takes longer, and we use a lot

more antibiotics.

So our patients would say that antimicrobial dressings are effective. There's really no resistance that we see, and they allow us to use less antibiotics.

Thank you.

DR. HARRIS: Thank you.

Our next speaker is Judith O'Grady.

MS. O'GRADY: Good afternoon. I'm Judy O'Grady. I'm the Corporate Vice President of Global Regulatory Affairs for Integra LifeSciences Corporation. My presence here today is being sponsored by Integra LifeSciences Corporation.

I would like to thank FDA for the opportunity to speak today. I'm very honored to be here. I would also like to thank and commend FDA for the excellent and informative Executive Summary as well as the presentations this morning.

My key points for the discussion, the 510(k) premarket notification has demonstrated to be an effective process to regulate wound dressings combined with drugs in the FRO category. Wound dressings with drugs are used for the management of wound care, not for the treatment of infected wounds and not for the treatment of infection.

There are wound dressings combined with drugs that have significant level of clinical experience, including clinical trial data and literature published in peer-reviewed journals. It's further recommended that a guidance document be established regarding special controls and contents of 510(k) premarket notifications.

The 510(k) process for wound dressings combined with drugs: There are actually over 700 wound dressings combined with drugs in the FRO category cleared by the 510(k) process. Medical devices regulated in the FRO category have indications generally for the management of wounds and wound environment, to increase [sic] bacterial load of the wound, not to treat infected wounds and not to treat active infections. Many of the

medical devices in this category have been regulated by this process for over 25 years, with over 25 use of safe and effective use.

Significant clinical benefit: While Integra LifeSciences manufactures several products in this FRO category, as well as we also manufacture products in the Class III categories that are regulated by FDA, significantly, there are wound dressings with chlorhexidine that are cleared for the indication for use through the 510(k) process to reduce catheter-related bloodstream infection. The CDC guidelines recommend the use of chlorhexidine-impregnated sponge dressings for temporary short-term catheters in patients older than 2 months of age.

Clinical trial results and articles published in peer-reviewed journals have established the safe and effective use of wound dressings with chlorhexidine. A randomized controlled clinical trial of over 589 patients demonstrated the use, the reduction in bloodstream catheter-related infections by over 61%.

The 510(k) process is an effective process. While it establishes substantial equivalence, as FDA discussed this morning, there is significant amount of data that's included in the 510(k) for these product lines. The goal is to demonstrate substantial equivalence but also to make sure that it doesn't raise any new questions of safety and effectiveness.

Data included in the 510(k): FDA reviewed this, but this is data that our company has actually included in the 510(k). They can be quite comprehensive: description of the device; information for use; cytotoxicity testing and acute dermal toxicity; sensitization studies; chronic toxicity testing; biocompatibility studies conducted under ISO 10993, which is an accepted standard by FDA; also in vitro microbiology activity; kinetic studies for the release of the antimicrobial from the wound dressing; in vitro zone of inhibition studies; performance testing, bench testing, animal testing, including clinical trial data for additional

indications for use or additional claims for the product; and then reference to the NDA for the antimicrobial agent.

As outlined in FDA's Executive Summary and in this morning's presentations, the General Plastic Surgery Devices Panel had an Advisory Panel meeting in August 2005. FDA presented information on dressings that contained drugs, silver, bismuth, chlorhexidine, and others, including risk of use, risk mitigation measures. The Panel voted unanimously to recommend that FDA classify wound dressings with a drug as Class II with special controls. The 510(k) process for wound dressings combined with drugs is an effective regulatory pathway.

Conclusions: Wound dressings combined with drugs currently in the FRO category should continue to be regulated as Class II medical devices under the 510(k) premarket notification process. We further recommend that an FDA guidance document regarding wound dressings with drugs in the FRO category be developed. There are many representatives today who --

DR. HARRIS: Please come to the conclusion of your statement, please.

MS. O'GRADY: Thank you. To work with FDA to develop these guidelines. Thank you.

DR. HARRIS: Thank you.

Our next speaker is Marissa Carter.

DR. CARTER: Good afternoon. My name is Dr. Marissa Carter. I am President of Strategic Solutions. But I'm also a clinical trial designer and manager. I'm an epidemiologist, a biostatistician, health economist, and EBM practitioner. So I'm kind of jack of all trades.

And one of the things I want to start to talk about is some major points that I think are missing. For example, complete wound healing, the only hard FDA endpoint we have, is

inappropriate for all these kinds of antimicrobial dressings. Current claims are based on containing infection and using the dressing as an antimicrobial barrier. Classic infection endpoints, in vitro data may be particularly useful. Some of those other secondary endpoints, and we'll talk about what those are, support real world interest by clinicians and patients. New treatments, yes. New treatments for topical antimicrobial products might justify risk assessment, in which case PMAs might be an appropriate route. But unlike antibiotics, we see no evidence of resistance is the problem in antimicrobial dressings, as we've already heard from other people this morning.

So let's talk about this: Efficacy for antimicrobial dressings in controlled trials, effectiveness in real world studies, it's not about wound healing. None of these products are designed to be treatments. The main goals, and especially if you go look at the claims on the products for these antimicrobial dressings, have absolutely nothing to do with complete wound healing.

And, in fact, if you go look as a statistician, as I am, you will find all of these trials virtually were not sufficient statistical power to do any analysis on this anyway because that was not their interest. So when you go look at these systematic reviews that everybody says, oh, there's no evidence on complete wound healing, it's irrelevant.

If you go look at these antimicrobial product trials, you'll find a lot of the currently used endpoints are not practical. In the real world, these are complex wounds, complex hosts. The practices that clinicians use are driven by the multiple needs of the patients and the wounds.

So classic infection endpoints, you know, where you measure quantitative bacterial counts and things like that, only make sense when antibiotics are not used. But since antibiotics are used virtually all the time, it's not very helpful. If you go look at safety endpoints in all controlled trials, again, none of those endpoints are helpful in

understanding resistance. But we have a lot of controlled trials of secondary endpoints of extreme interest, things like odor, pain management, and exudate management. These are targets not only for controlled trials but also for the real world.

And this slide is just taken from some early silver-impregnated dressings. Everywhere you see that box, statistically significant, SS, that's a statistically significant secondary endpoint. And I would submit to the Panel that these secondary endpoints that are almost ignored a lot of time, things like exudate management and odor and so forth, should be, in fact, the primary endpoints of these trials.

Look at the claims. Current claims are based on preventing spread of infection or being an effective antimicrobial barrier while the dressing does its job, maintaining moisture barrier, absorbing the exudate, and so forth. However, if different claims need to be brought forth, then we might require different endpoints.

So my recommendation is keep these antimicrobial dressings as Class II medical devices under the PMA. Most of the evidence we have to date suggests very low risks that are virtually understood. And if we need different claims for different products, well then maybe we need to reassess risk and think of a PMA then. And this may be appropriate also when we have a novel mechanism of action.

Resistance: We have multiple resistance mechanism -- sorry, multiple mechanisms of action, and you've heard this from a number of people, including Dr. Wolcott. Controlled trials are not a way for us to understand resistance of microbial agents. And most of the time, we have minimal or no resistance anyway.

So I would suggest the path forward is we have probable benefits and relatively low risks, and the whole resistance thing is mainly about antibiotics and not about antimicrobial agents.

And thank you for your time.

DR. HARRIS: Thank you.

Our next speaker is Caroline Fife.

DR. FIFE: Thank you. I'm Caroline Fife. I am a Professor of Geriatrics at Baylor College of Medicine in Houston, Texas. I am the Executive Director of the U.S. Wound Registry. I've been a wound care clinician for three decades, most of it in academic medicine in the Houston Medical Center. And I am the Co-Chair of the Alliance of Wound Care Stakeholders.

And the main thing that I'd like to focus on today is why the answers that you seek are not going to be found in the randomized controlled trials where you've been looking. The problem that we have is that real patients don't look at all like the patients in RCTs. Dr. Carter and I have performed an analysis of this and found that when we looked at about 8,000 real-world patients, more than 50% of them would have been excluded from virtually every RCT that had been performed in wound care in the last decade because most of those RCTs exclude patients with comorbid conditions because of the difficulty in stratifying patients by risk.

The average wound center patient is more than 60 years of age, has wounds that have been present for 6 months at the time of presentation, and has at least six major comorbid diseases, with 30% of those patients, approximately, having diabetes even though are not being treated for a diabetic foot ulcer, about 5% of them having renal failure or a transplant, and about 8% of them being on steroids.

And so as a result, we have been analyzing data from the U.S. Wound Registry, which is a nonprofit organization that has no sponsors and no support from a specialty society and, I'm sorry to report, also receives no federal grant money. It is data that has also been -- it exists in order to provide quality data for physicians participating in PQRS since 2008. Since 2014, we've been a QCDR.

We have developed 21 wound care related quality measures, as Marcia alluded to, in conjunction with the Alliance of Wound Care Stakeholders, including high priority measures such as patient-related wound quality of life and patient-reported wound outcome.

And we also, we receive data directly from electronic health records that includes detailed descriptions of a wound at each visit, including drainage amount, odor, color, the appearance of the wound. And we also have data on every dressing change that is performed at 130 hospital clinics, where we have more than 1.5 million individual dressings and about 2 million patients in 34 states and Puerto Rico.

We know the duration over which dressing was utilized and the details of other medical therapies and whether the wound changed in response to those treatments and whether there were any difficulties encountered.

About 7 years ago, the Alliance of Wound Care Stakeholders sponsored one of the only analyses of the use of antimicrobial dressings that's been performed. We looked at more than 5,000 patients with more than 7,000 wounds. And in the real world, only about 66% of these wounds actually heal, with an average time to heal of over 100 days and 10% of those wounds taking more than 33 weeks to heal.

And I should add that in the real world, most of these patients receive at least five or six different categories of dressings during their time in wound care; 71% of wounds are treated with an antimicrobial dressing, and 4, almost 5% of wounds receive four or more different episodes of antimicrobial dressings of different types.

As I mention, the wounds have been present for 6 months by the time an antimicrobial dressing is selected. And there are criteria that clinicians appear to use when they select an antimicrobial dressing, such as patients having multiple comorbidities, the wound not appearing to have evidence of healing, and systematic antibiotics also being utilized. And the antimicrobial dressings tend to be used for about a month's time.

We evaluated the types of antimicrobial dressings and their pattern of use and found that about 20% of antimicrobial dressings are silver-based. About topical prescriptive antibiotics though, these are antibiotics put topically into the wound, are used about 9% of the time, cadexomer iodine about 4% of the time, and honey about 3% of the time.

So we have the ability to risk stratify wounds with a predictive model, and it appears that antimicrobial dressing use is high because the wounds appear to need it; 80% of these encounters document large to moderate drainage, and 52% of these patients are prescribed systemic antibiotics. Most of these patients get even more than one course of systemic antibiotics, many of them intravenously.

So we have the ability to monitor changes in treatment, systemic antibiotic practices, and we can answer many of the questions that have been posed here about the use of antimicrobials and their relationship to hospitalization, amputation rate or healing rate, assuming that there was funding to do this kind of work. But sadly, there is no such funding, and therefore, we cannot answer your questions, I'm sorry to say.

Thank you.

DR. HARRIS: Thank you.

Our last public speaker is Susan Alpert.

DR. ALPERT: Thank you. Good afternoon. I wanted to first thank the Panel for your very insightful questions and deliberations so far, and look forward to hearing some more.

I'm Dr. Susan Alpert. I'm actually a microbiologist and pediatric infectious disease specialist. I spent 13 years at the FDA, for 6 of them in the Anti-Infective Drug Division that you've been hearing from this morning, and for 6 years I was the Director of the Office of Device Evaluation.

So what I want to do, in the 5 minutes that I have, is talk a little bit about these products and how the tools that are available to FDA can be used to address the things that

are concerning about not having these products, these pre-amendment products -- although most of them are post-amendment products, products like these were pre-amendment products, and that's how the process works and how they could, and I think should, be regulated on a go-forward basis.

You won't be surprised, those of you who know me, that I'm actually going to read so I can stick to the 5 minutes because otherwise I could talk for a very long time.

So there are many types of products that are in the FRO category, and FDA very appropriately has asked you to look at least at three different categories of them, slice and dice them a little bit into three because the products are really very different. Even though they all are directed at wounds and they all contain some type of antimicrobial agent, they are very different. Washes are very different from bandages are very different from the ointments. And FDA has asked you to take a look at that.

Important to understand that FDA classifies intended uses. What's the product used for? Not the product itself, but what's it used for, and what are the benefits and risks of that use? And then the company brings in data that says, this is my use, here's the efficacy data, here's the safety data, here's what I did to test my product, and here is why it meets those criteria. So that's number one.

I want to talk or actually remind you a little bit about the benefits. You've heard them from the last couple of speakers. Important to remember that these products are not treating infection, not topically, not systemically. The antimicrobial materials that are in these bandages are not intended to be absorbed by the body and used to treat infection. They really are to manage the environment, to manage the environment on the bandage. That's a really important part of understanding why they're used for chronic wounds.

Exudate and bacterial contamination of the exudates, which winds up on the bandages, are annoying to the patients and a challenge for their healthcare providers. The

body can heal the wounds, but not if there's a lot of exudate that's contaminated with bacteria in the way. You've already heard the mechanisms by which that happens.

Keeping the growth of the bacteria on the bandage down helps the wound and helps the patient. Both patient-centric measures, like exudate and odor, and healing mechanisms, by keeping that amount of bacteria that could be building up on the wound from the bandage, sitting and growing on the bandage -- because the bandages are not something that you change every few hours. These are bandages that stay in place for a while. That environment exacerbates the chronicity of the wound if it's filled with bacteria. So these bandages are intended to help the environment in which the wounds are trying to heal.

To appropriately understand where to place these, you have to look at benefits -- we just talked about those benefits -- and risks. So let's talk about the risks. You heard a little bit about the MAUDE database. What we didn't hear is which patients were the ones that had the serious outcomes, because some patients that are treated with FRO products are patients with indwelling lines. Some of those do get infected, and those patients can be very sick. They can become septic; they can die.

We need to really understand that we're talking about -- when we're talking about the topical bandages for chronic wounds, we're not talking about those kinds of infections in patients. So we really need to understand what's in that MAUDE database and which products the real high risks are associated with so we can really understand what we need to be looking at.

What are the more common adverse events associated with these kinds of products? Stickiness on the wound, we know what to look for. Chronicity, the wound not healing, well these wounds don't heal, and the people who manage them understand when they're going even slower, when there might be some local toxicity from the bandage.

Wounds change their appearance; they change their microbial load over the time of the wound. Care changes. Products used on them changes. The types of bandages change. It makes it for a very challenging environment to do the clinical trials in, but that's what we're doing.

And we need to look at the resistance issue. I'd say two things before I finish. The first is that the use of these products, by keeping down the bacterial load on the bandage, can decrease the amount of local and systemic antibiotics that are used in this patient population. That's directly related to the issues around resistance because the resistance doesn't come from these products; it comes from the systemic antibiotics that are used.

These products, the materials used on these products attack bacteria in more than one site. They don't lead to simple one-step resistance. It's not the kind of resistance that is passed from one bacteria to another. We need to be able to develop that data. That data will not be developed in randomized clinical trials. It will be developed in real-world data, looking at very large datasets, to be able to look at the different patient populations, the different etiologies, and the different ways in the way patients heal.

I want you to just think about that tomorrow as you go to classify the products. Thank you.

DR. HARRIS: Thank you. So I now pronounce the Open Public Hearing to be officially closed. And I invite Commissioner Califf to give a formal charge to our Committee.

DR. CALIFF: Thanks. This has been an interesting day already. I think it's going to get even more interesting as we get into the discussion. Just a few notes and preamble from things that I've read and heard.

First of all, this is a much more common problem than most people know, and I know members of the Panel are aware of this. But if we just think about 1 to 2% of the U.S. population, that's 30 to 60 million people. This is not -- 3 to 6 million, I'm sorry. This is not

a tiny group, 3 to 6 million people. And the cost alone of wound care is estimated at about $50 million annually. So when we think about resources needed to clarify evidence and the consequences of having the best evidence, both for health outcomes and for our strained healthcare system, there's a lot at stake in doing the best that we can.

We've heard people in the last hour talk about something that we agree on. We're not here today to talk about the totality of optimal wound care management, although we know that it's important, and we have to keep that in the background as we have our discussion, realizing that the products that we're talking about are just one element of a much more complex system.

But I've also heard a very mixed picture on the data. You know, I'd have to say, having looked at a lot of fields of medicine, in particular, in the last year and a half, getting to look at just about every field of medicine, this seems to be an area where the quality of the evidence is just not up to par compared to the average of what we see. And, you know, I, for one, would accept that these are complicated patients, difficult circumstances but you know, what patients are not complicated? You know, cancer patients are complicated. Chronic vascular disease patients are complicated, etc.

And so I think a question for the Panel is given the difficulties that have been described, how would we go about collecting and understanding the best evidence that we could get?

We've also heard that we agree this is not about treating infection. Products that are intended to treat infection have already been classified as being in a category that would require rigorous studies. We heard about one such product in the introduction that's recently been approved.

But I'd also add, the third part of our mission, which people don't talk about as much, although it comes up every day, is explaining how to use products to the variety of

people to whom this needs to be explained. And what I've heard today is sort of a mixed story. Although the products are not labeled to treat infection, we look at the registry data. It seems pretty clear to me that people are interpreting whatever they're getting in these indications in a variety of different ways, some of which are getting pretty close to the intention to treat infection. So how to understand that in the context of the evidence, I think, will be important.

And then there's the fact that these are pre-amendment products. So as has already been described, it's hard to say that we have reasonable assurance of safety and effectiveness when we're comparing new products to products that were never tested in the first place.

And I've heard there's a lot of confidence in the clinical community about this, and a lot of personal experience, but as I like to say, when I put on my clinical practice hat, I'm just a country cardiologist from South Carolina. And we sure learned in cardiology that about half of what we thought was true turned about not to be true when it was put to rigorous testing, and no one could predict which half was true and which wasn't. And so I would urge the Committee to think carefully about, particularly in such a complex clinical environment, how well you can really tell that an individual product is having the intended effect, among all the other things that are going on with the patient.

So in our charge today, and this next part of the Panel meeting, you're going to be asked to discuss the types of clinical evidence, including the design of comparative effectiveness studies that would be necessary to support certain indications, as well as appropriate controls necessary to understand how to mitigate the risks to health and assure the safety and effectiveness of wound dressings combined with drugs.

As we've looked at it, our read of the data available is that there's not agreement on how to optimally dress a wound. And this is puzzling to many of us given the magnitude of

the problem I've just described, if it's affecting so many people. And although I've also heard that we're doing pretty well, I don't think anyone would argue that if you look at the population of patient with chronic wounds, as an example, the mortality rates and major morbidity rates are quite astounding. No one's attributing these as adverse events to wound dressings, but surely we could do even better if we had more clarity about what worked and what didn't in this environment.

And we know that adding antimicrobials to a dressing adds to the possibility or probability of certain toxicities that have been described, although I think most people agree the rate is relatively low. But typically, in therapeutics, when one has adverse effects, one looks for offsetting benefits that are clearly understood and described with high quality evidence.

So with that background, we look to your expertise to provide feedback on the endpoints of interest, again emphasizing we're not looking at dressings intended to accelerate wound healing; that would by definition be Class III.

What kind of evidence will be necessary to support adding an antimicrobial to a wound dressing on an uninfected wound, something that's been discussed in general and now the Panel should take it up. And we're really looking to your expertise, both clinically and with regard to evidence in this field, to help us understand it.

Do you see any clinical utility to the concept that one might try to reduce colonization of the dressing itself, treating the dressing as opposed to treating the patient? What is the utility?

What kind of systemic absorption data are necessary for products added to a wound dressing?

Are there barriers to conducting RCTs? We've certainly heard there are. But I think we need a thorough examination, because in most fields of medicine, randomization brings

a degree of clarity. I think there's often confusion about heterogeneity of a population. The way to deal with heterogeneity is to randomize because that balances the pre-existing risk before the inception time of the treatment.

Having said that, I do want to give a shout-out to what we heard about registries. I personally started my career with registries. I'm a big fan. The FDA is very much in favor of registries. CDRH, in particular, is advocating and pushing for registries as a great way of doing business. But I'd also add that a major part of therapeutic evaluation today is the use of registries as a basis for randomization within the registry when there's a question, where a modest difference in treatment effect might be expected.

And then finally, in terms of risk, I want to remind everybody, it is the position of the government right now, that is, HHS and a presidential initiative, that all antimicrobial use should be limited as much as possible; that is, given that there's a societal risk to any use of antimicrobial agents -- and I had to step out for the presentation from Europe, but there was certainly an implication there that the restriction, a watch radius of antibiotics for wounds may have had an effect on reducing MRSA, for example, in their intensive care units.

Given that there is a societal risk, we really need, as much as possible, to understand the benefits before we begin to advocate for the use of antibiotics. This was an Executive Order, September 2014, and it's going to be a topic of even greater discussion, reminding you again that under FDA policies that took effect January 1st, antibiotics considered medically important for humans are no longer approved, for example, to promote growth in livestock. And farmers now have to get a veterinary visit to the animals, something I've heard a lot about because of the very widespread concerns.

And so I think an issue for the Panel is what role in such a large -- 3 to 6 million people -- in our population would the use of these products play in antimicrobial

resistance? It's been interesting to hear different views.

We're coming in, having reviewed the literature, but you're here because we need to learn from you about what you think as experts in the field. And we'll always be willing to change our opinions based on the best available evidence, and look forward to the discussion today.

DR. HARRIS: Thank you. So we have a tall order before us. In the next 45 minutes, ideally, we'd like to provide some feedback and discussion that'll be useful to FDA and hopefully summarize our Panel's opinions regarding this first question, which is actually a series of questions.

I'd just like you to know that we are not, ideally, going to be asking questions of FDA or industry at this particular point in time, unless there's a burning need to do so.

If we could put up the first questions on the screen there. And what we'd like is -- I beg your pardon? We'd like to have everyone when they -- yes?

DR. SAYEED: Dr. Harris, before we start the Panel question, I do have a burning question for the FDA. It's a kind of a two-part question, if you'll bear with me for a couple of minutes.

DR. HARRIS: Is it absolutely essential to be done now?

DR. SAYEED: I think it's relevant to the Panel --

DR. HARRIS: Okay.

DR. SAYEED: -- questions.

DR. HARRIS: Please.

DR. SAYEED: So effectiveness is based on clinical outcomes. Efficacy is based on the inclusion of controls, at the minimum, matched controls. In terms of Class II versus Class III, my question for the FDA is, you know, a Class III device, you could have a higher level of evidence. You could ask for randomized controlled trials; it would be more generalizable;

you could look at healthcare disparities in populations.

In Class II devices, you may not get that level of evidence. What reassurance can the FDA give the Advisory Panel today that postmarket analysis can be done in a timely manner? You know, the GAO report came out that said that maybe 20% of devices aren't evaluated in the postmarket analysis in a timely manner within 7 years.

And then I also would like to know, in terms of the role on the consumer -- Dr. Califf had mentioned that -- as a consumer representative, you know, the burden to the consumer is very high. If these products are increasing resistance and cost to patients, you know, if there isn't a lot of evidence, why are we asking them to pay it? So, thanks.

DR. ASHAR: I have some brief responses to that. First of all, I think, when we look at valid scientific evidence, that's a regulatory term, and there's a long definition associated with that which we can cover tomorrow as we make, as the Panel deliberates over a possibly Class II or Class III.

So I think the focus of this discussion right now are some of the scientific issues rather than focusing on the classification. When it comes to valid scientific evidence, we do look not just at controlled trials, but we could look at single-arm studies, we could look at well-collected case reports of experience. It depends, in some sense, on the benefit/risk profile of the medical device at hand. So we do consider under the term "valid scientific evidence" a large body of evidence that will help inform us.

And I think, what was the -- oh, the second point I wanted to make is in your deliberations this afternoon, FDA does not consider economic aspects of wound dressings. I know that's come up quite a bit. As you determine the value of these products, we're talking about the benefit/risk profile, the safety and effectiveness profile, but not the economic value of the actual product. So discussions along those lines should not be part of the conversation this afternoon.

DR. CALIFF: You know, just to quickly amplify on that, my discussion of the cost of all this is really to point out that this is a resource-intensive effort, where some portion of resources going into evidence generation, to clarify, would be useful. But we're not to consider price in any of the deliberations. It's risk and benefit that should be considered in these discussions.

DR. HARRIS: Thank you. So I believe that Dr. Chang is going to -- oh, no, not Dr. Chang. Dr. Durfor is going to read the questions for us. Is that correct?

DR. DURFOR: Yes, sir. That is correct.

Question Number 1: Products under product code FRO that are the subject of this Panel meeting include: 1) solid wound dressings combined with drugs which are intended to provide or support a moist wound environment, absorb wound exudate, and protect against external contamination; 2) wound gels, creams, and ointments combined with a drug which are intended to provide or support a moist wound environment; and 3) wound wash solutions combined with a drug which are intended to rinse or irrigate a wound to remove foreign material, such as debris and wound exudate. Clinical data have not generally been required to support clearance of wound dressings in product code FRO.

These dressings may be combined with different categories of antimicrobials, for example, 1) metals such as silver and bismuth, 2) biguanides such as PHMB or chlorhexidine, 3) quaternary ammonium compounds such as benzalkonium chloride, and 4) oxidizing agents such as hydrogen peroxide and hypochlorous acid/sodium hypochlorite that are claimed to:

- improve the shelf life of non-sterile products;
- permit the repeated opening of a container after the sterile seal is broken;
- prevent bacterial colonization of a dressing; and/or
- provide a barrier against microbial entry into the wound.

Let's see, is this the slide advancer? Thank you.

Question 1a: Is there adequate scientific evidence to demonstrate the safety and effectiveness of FRO products for these different uses? Are there data from well-controlled trials? And if not, what type of scientific evidence exists?

DR. HARRIS: Dr. Wolf.

DR. WOLF: You get what you pay for. And there is no national institute of wounds. There is no national institute -- there is no research body that is in the federal government that is charged with getting information along these lines.

If you look at AIDS, for instance, hundreds of thousands of dollars of federal research support have been given, per instance, hundreds of thousands of times more dollars per instance than it is for wounds. And so that's why we don't know.

Are there any good -- are there any data from adequate, well-controlled trials? In burns, I can tell you no. There is not. And I would know.

And if not, what type of scientific evidence exists? Some, you know, cohort trials. There's the occasional trial that's done mostly out of the Netherlands. Seems to be where a lot of this stuff has been done. Why? Because their government is funding it. And there are -- I'd tell you, I reject 70, 80, 90% -- I mean, I reject seven, eight trial studies every day of some new wound goo they were going to put on somewhere that's going to help somebody. And most of that doesn't see the light of day.

And so I'm sorry to get on my -- immediately get on my soapbox. But we don't know because we don't ask. And we, as a society, we haven't given a priority to finding out these things.

So, as a clinician, I'm going to put my clinician hat on, what are we to do, then? The best we can. And what we've got now is some products, which many of them seem to be doing okay. We sometimes tend to disregard the marketplace as a signal for what actually

works.

And, you know, in cardiology and things like that, we've had -- you know, when the stents first came out, that was wonderful. Why? Because the alternative was almost I was going to cut his chest open. And so people said, hey, can you do something different than that? And so there was a lot of interest in that. There are many, many, many other advances in cardiology which didn't involve anything like that that were very, very good. But there is a National Heart Institute.

And same thing with many other of the things that we've got. So my point is from as far as the -- to answer this specific question, is there adequate scientific evidence to demonstrate safety and effectiveness of FRO products in these different uses? No.

DR. HARRIS: Dr. Sood.

DR. SOOD: Thank you. I think that was very -- this is Geetika Sood. I wanted to just share my personal experience in trying to develop a trial to look at wounds.

I am interested in wound microbiome, and we were looking at surgical site infections, comparing one dressing to another. The reason that I'm bringing this up is to follow up on what Dr. Durfor was talking about in terms of the challenges of doing a clinical trial. Certainly, that would be an ideal situation, to balance out all the confounding and effect modifiers.

For us, in a patient population with very limited comorbidities, with a relatively reasonable rate of surgical site infections, to power a study to be able to test any kind of difference, you were talking about thousands of patients. So I think, while we all agree that a randomized controlled trial would be a wonderful way to collect the evidence that we need, the actual logistics of trying to do that, when you expect maybe a 5, 10, 15% improvement in wound healing, is going to be a very large logistic endeavor.

DR. HARRIS: So I just want to make sure that we're addressing Question 1a.

Question 1a is asking us are there data from adequate, well-controlled trials to support the indications for use for these dressings, which were shelf-life extension, protection for repeated use, to prevent the product itself from becoming contaminated or colonized, and to provide an effective barrier for the wound?

So I think that all these things you're saying are very, very important. I think we'll probably get to some of that later, but I just want to restrict our comments to the answering that is it adequate data, and secondly, if not, what type of data does exist.

Dr. Holmes.

DR. HOLMES: Thank you, Mr. Chairman.

From my perspective, with respect to the four claims, yes, there's adequate scientific evidence to demonstrate safety and effectiveness. And you don't need well-controlled trials to demonstrate any of those. Those are all things that can be done in the lab, period. And special controls can further direct and manage any risks that might develop subsequent to that.

So it's very clear that, you know, from my perspective, the answer to this question is yes.

DR. HARRIS: Any other comments? Yes.

DR. MILLER: I appreciate that comment. I totally agree. You don't need a clinical trial to answer any of these questions. If you want to ask if any of the things matter for getting the wound to heal, now that, you need a clinical trial for. You know, but if we're restricting ourselves to these four issues, I don't think that's very ambiguous, that these are addressed by the antimicrobial-laden dressings.

DR. HARRIS: So not to put anyone on the spot, but Ms. De Luca, what do you think?

MS. DE LUCA: Well, from a patient point of view, I've been feeling that we're not covered. I don't think the patient recognizes that anything is being done in this country for

the wounds. I think a lot of us have wounds. I, for instance, secondary to the wound/wounds from surgery that I've had for multiple diseases, I have an ostomy. Nobody's mentioned that huge population. That's an active wound in our lives every single day. I spend three or four times in the ER every year from it. And that's just the tip of the iceberg. I think that there's more that we could do. It may not be a clinical trial, but somebody could do a compilation of trials, and let's at least start with that and find out where is the data? Where are we at?

DR. HARRIS: Oh, sorry. Dr. Hickerson.

DR. HICKERSON: One of the problems that we have with the controlled trials, when we say that we can randomize, and that takes care of everything, yet when you go to try to study this, there's a lot of patients that we're told we have to eliminate from those studies by the FDA. No, you can't put this patient in. You get a study that you're wanting to do with anything that you're doing on the skin for a burn. Well, it can't be an electrical injury. It can't be a chemical injury. It can't have an electrical injury. They can't have diabetes.

So we're already taking a lot of those out. And so I understand, so I agree with Dr. Wolf that we don't have those well-controlled trials. And I agree with Dr. Miller and Dr. Holmes, we really don't need for the safety aspect nor for the effectiveness of what we're discussing today.

DR. HARRIS: Dr. Alam.

DR. ALAM: To address the question, in my opinion, they are not very large, well-controlled trials, as others have said. There are cohort studies. There are small clinical trials. And there is patient and physician consensus in various consensus documents, and patient satisfaction associated with the use of these devices in some cases.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: But that's for wound healing. What we're talking about here are the

four claims under 1a in the question. And those are just benchwork claims.

DR. ALAM: I understand what you're saying. I'm just trying to go with the letter of the law. They're asking if there are adequate well-controlled trials, and I think the answer has to be no. I agree with you; it might not be relevant. But I think the answer is still no. But I would suggest that even in the clinical setting, in addition to the in vitro studies, there is a preponderance of information suggesting that some or all of these devices have clinical utility. Does that --

DR. HOLMES: Yeah.

DR. ALAM: -- agree with your position?

DR. HOLMES: Oh, I mean, there's no question there's a paucity of evidence across this entire field, I mean, burns, in particular. And, you know, I'm never going to argue that. But in respect to the four claims, okay, there's no clinical evidence. Guess what, you don't need it.

DR. HARRIS: Commissioner Califf?

DR. CALIFF: Yeah. Just a quick response to the inclusion criteria comment. It may be the case that in some instances the FDA is telling companies to restrict entry criteria, but in most cases, that's not the case. And, in fact, a key priority, if you look, go to CDRH's website and look at priorities for this year, one is to increase inclusiveness in clinical trials. And I would urge the clinical community, to the extent that you think broader trials with more representative populations are in order, that you get together with companies, and I'll bet you find the FDA is very receptive to that approach.

DR. BURKE: I agree that given the four criteria here, as far as treating things on dressings, that's all in vitro testing. The main problem we are worried about is resistance, and I don't know that any studies have been -- perhaps the studies have proved all of the above four criteria, but have any of the in vitro studies looked for the development of

resistant organisms? Because that is by far the most difficult side effect and the thing we don't want.

And perhaps if those studies show no development of resistant organisms on these bandages or products, then I think that's an excellent reason to feel better about the safety.

DR. HARRIS: So I'm going to actually just kind of move us forward a little bit because I think that Question 1a, we've kind of addressed. It sounds like, unless someone, of course, has a very, very passionate disagreement, that we've agreed there are no well-controlled trials, but the question has been raised whether or not that's actually necessary to confer the efficacy with respect to these four specific areas, and that the type of scientific evidence that does exist is essentially in vitro testing.

DR. DURFOR: Question 1b: If there is adequate scientific evidence to support the use of FRO products for different uses, on what endpoints are they based?

DR. HARRIS: Any comments? Yes.

MS. LOTT: This is Michelle Lott. Actually, Brandon, in his presentation, went over some very specific laboratory and benchtop testing that would be meaningful endpoints to quantify some of these very things, you know, being the simulated use testing. He mentioned the modified AATCC test method, the USP <51>. There are some, you know, recognized consensus standards on shelf-life testing and some different tools that are already existing that could be easily incorporated into a special controls document.

DR. WOLF: So I agree, Jimmy, the first two of these can easily be done in vitro. The other ones can't. You got to put this dressing on somebody's 400-pound guy, on his back, when he's laying in pus, to see if it actually does what these things say it's going to do. That's going to require clinical testing. Now --

MS. LOTT: But back --

DR. WOLF: But for the first two, yes, what are the packaging --

MS. LOTT: Back to those four specific things, though, for those four specific items.

DR. WOLF: The last two, to prevent bacterial colonization of the dressing, when that dressing is underneath a guy on a bed, that's when we want to know that it's doing, not on a benchtop, right. Because a benchtop, we're not treating the benchtop. We're treating the patient. And so we got to put it in the condition that it's going to be used, not in an in vitro condition, as I want to point that out.

The second thing is that I want to reiterate Dr. Califf's point about data collection. And I really like the idea of we can answer that question probably with what the econometricians are doing now, is you get big data, and you can really, you know, you can parse that stuff out and do some of these things like that. And maybe that's the answer is to get at it that way. And then you include all the different patient groups and not just the one that you can get to sign a consent form.

DR. HARRIS: Dr. Hunt.

DR. HUNT: I agree that a lot of the data that's available is from preclinical testing, in vitro testing, and that probably does answer many of the four things that we talked about. In terms of the clinical question, though, the endpoints that have been used so far are probably not sufficient to be able to answer any of the questions.

So probably that 400-pound patient that you're talking about who's laying on their back with a wound, who has a dressing that it's intended to reduce bacterial contamination, you know, that you can measure it, but at what point do you decide that it has failed? You know, how long is it sufficient? Does it keep the patient from having to go on IV antibiotics or proceed to some type of operative debridement?

You know, there's many different endpoints that really need to be evaluated with respect to this because this is not intended for a curative approach per se.

DR. HARRIS: Dr. Burke.

DR. BURKE: The problem with the clinical endpoint is there's no control. I mean, do we have another 2-, 300-pound patient on his back with an ulcer? Was Patient A infected and Patient B not? Did Patient A have diabetes and many comorbidities? Was one patient 80 years old and one patient 30 years old?

So it's just so difficult to have a clinical endpoint. I mean, we don't know how to define it, and we can't do the controls. And the heterogeneous population of -- some people have had oral antibiotics, some people are on immune suppressives, some people have damage from radiation dermatitis. So it's just so difficult to do a control and to determine an endpoint.

And I just sort of suggest that, first of all, as far as the in vitro studies, those can be done with very high criteria. The 510 criteria are excellent. And as a physician, as physicians, we treat individual patients, and we just have to remember common sense.

DR. HARRIS: I just want to reiterate that I think we're -- and it's difficult not to blend issues of patient treatment versus --

DR. BURKE: Sorry.

DR. HARRIS: -- preventing the dressing from becoming colonized. As I understand it, we're really being asked about are the addition of these chemicals impacting the dressing, not the patient?

DR. ALAM: Yeah. To address -- this is Murad Alam. To address the Question (b), as what endpoints they're based on, and based on a talk we heard earlier, Dr. Gottrup, the endpoints include wound closure rates, healing time, and the other outcomes are wound reduction rate and change in wound condition. Of course, that applies to the clinical aspects, but if you go back to look at the fourth item under level of evidence, it's provide a barrier against microbial entry into a wound.

So that is actually that even though it is pertaining to the functioning of the material,

it does require placing it on a wound, I think, to determine if that's the case. And those are the most common endpoints based on an assessment of outcomes. As to how valid they are, I'm not really sure.

DR. HUNT: That's my comment, I think. Before, previously, what I was trying to get at is, like if that's your endpoint, how long is that dressing -- should be ineffective for you to say that it is useful or not, and when did it fail or not? So I think that those endpoints are not well defined. Just saying bacterial contamination, I think you have to define over what period of time, and what's a reasonable time frame for that to be considered before you have to change management.

DR. HARRIS: Commissioner?

DR. CALIFF: This is making me wish I was back being a panelist on the --

(Laughter.)

DR. CALIFF: It's fascinating, and it's great to hear how your minds are working. I just -- you know, part of my response to the thing about no control, you know, with all due respect, I can accept that trials are hard to do, but the way you get controls for the 400-pounder is to randomize a population of patients. And that's what randomization does is it equalizes those risks as a method of study design.

So I think we'll have a discussion later about what the barriers are to doing that, given the fact we have millions of people who are eligible for randomization who are under medical care in a fairly intensive environment.

And then I do think another difficulty, we've got these four claims here. But the remit to the FDA is safety and effectiveness for the patient. And so I think we might ask for a comment from CDRH here, because I think part of the complexity here is I think you're responding quite well to both sides, and it's hard to not mix them. But part of this is to understand what the link is. For example, shelf life of a non-sterile product, I mean, I

presume the reason the shelf life is important is because if you go beyond it, it would be a danger to a patient.

And so I think part of what this may be intended to get at is, is there a meaningful measurement of shelf-life extension that would signify that it makes things better for a patient or that there's not some risk that's occurring? And you could go through these four and look at them the same way, but --

DR. ASHAR: Yeah. This is Binita Ashar. I also had a comment. I think, as we're going through these questions, the one thing to keep in mind is the way that we're regulating these products in CDRH is based on the given intended use or indications for use that the sponsor comes to us with. So they will tell us it's a barrier or that, in general terms, it's a preservative for multiple uses or it's to create a moist wound environment.

And so these questions are really intended to get at the testing that's necessary to support such claims. We will, in the subsequent questions, Questions 3 and Questions 5 especially, start talking about the extent to which these sorts of claims are clinically relevant. And so I think that that -- and actually, the way that these were constructed were intended to walk you through it, to get into the deep end more gradually, but you've just jumped right in.

(Laughter.)

DR. ASHAR: So some of the comments, I think, will be very -- things that you're discussing now will be helpful for Questions 3 and Questions 5.

DR. HOLMES: Dr. Kitchel presented very well, earlier, what endpoints all of these are based on. And I mean it's very clear that there are both industry-accepted and FDA-accepted lab tests to substantiate these claims. Next question.

MS. LOTT: And, you know, to speak to some of Dr. Wolf's claims about being able to take some of those lab tests and then simulate, you know, something closer to clinical use,

you know, in many other applications, it's standard practice for sample conditioning and different things like that. I could see how some minor modifications to some of these test methods could give an engineering simulation of possibly that 400-pound patient, of some pressure distribution testing, some heat testing. There are a lot of different methods to prepare a sample in a way that gets at more similar to its anticipated use.

DR. WOLF: Oh, I got that, but as I tell my fellows all the time, the best model of human disease is, in fact, the human. And so maybe we should be using -- because we have millions of people with this problem. There's no shortage of potential subjects. And we're not talking about things that are particularly harmful, we don't believe, right, and that subjects will sign up for these kind of studies.

And so that's really what we should be trying to do. The first two, of course, you can't answer that anywhere but on the benchtop, right. But when you start talking about wounds and the relationship of the wound to the dressing, you have to do experiments.

DR. HARRIS: Dr. Miller.

DR. MILLER: I think, to answer these questions, if you're not satisfied with an in vitro test for questions 3 and 4, then the control for those is a dressing with the antimicrobial and one without. That's the control. And then you confirm the answer to the question. It shouldn't be a difficult study to do, if you want to do it clinically.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller. These items that have heretofore been discussed as measurable and adequate scientific evidence, in the end, are only surrogates for what we're really interested in, in the healing of the wound in the patient. And unless there are data to support their surrogacy for those endpoints, there's no way of knowing.

And I was happy the comment just made because, you know, I'm not convinced, until you have the same vehicle, product, gauze, pad, with and without whatever ingredient, that

one knows what is happening because some of these things -- I don't doubt that hydrogen peroxide will inhibit or kill organisms, certainly hypochlorite solutions. But that is another matter with what their effect in toto in application clinically is. Because some of these things that have been used for many years, people are raising questions about what do they do to the tissue. And I think, with and without the putative, primary active ingredient is the only way to know.

Now, one can get into -- later on -- and maybe I'll save discussion for that -- in terms of the size of the trial and what would be necessary, etc., there are different mindsets of approaching those things that are currently not being done, I don't think. But, you know, we're talking about things that are easy to measure but are surrogates, and they don't get at what we're really after clinically.

DR. CALIFF: As an example, just to pick on one of these, and it sounds like you all have already answered this, but how do you decide that you've done enough to know that you can permit repeated opening of a container after the sterile seal is broken? That's a claim.

DR. SAYEED: I wonder that all the time, whenever I open up my Neosporin or something, because, you know, when I -- let me give you an example. When, in interventional pain, when we use lidocaine, to use local anesthetic, I discard the bottle after every patient use. I'm surprised that we don't do that in wound care.

DR. BURKE: But I think that's measurable. In other words, to answer that, Part 1 is you, under certain conditions of temperature and light, UV light, one could measure the sterility after 50 openings, 100 openings, etc. So in other words, that's measurable. And after making measurements, you could decide what is your cutoff, what is your endpoint criteria. And I'm sure that that has somewhat been done.

I know the cosmetics industry has certain guidelines for opening and the conditions

in which it's opened and --

DR. CALIFF: Thank goodness we won't be discussing cosmetics today because --

(Laughter.)

DR. BURKE: Yeah.

DR. CALIFF: But --

DR. ALAM: Can I --

DR. CALIFF: I think part of the intent of this question is, is do you all agree that there are criteria by which one could make that claim? Is that --

DR. ASHAR: Yeah, absolutely. Sorry, this is Binita Ashar. I think Brandon Kitchel outlined some of the information that we look for when we evaluate these claims, but any additional things that we should be looking for would be very helpful to us.

DR. ALAM: And we've done studies, not for product approval, but just to assess for our own hospital the consistency and safety of multi-use vials. And we've done them naturalistically, where we've had a multi-use vial, actually hundreds of them, reconstituted, put into a refrigerator, and have this sort of simulation whereby a number of people access it with syringes and take out a certain amount of it on repeated days. And then at the end of X hundred such uses for X hundred vials, then those are cultured.

And so that's, we think, a reasonably systematic way of doing that. I don't know how FDA does it though.

DR. HARRIS: Mr. Kitchel.

MR. KITCHEL: Very briefly -- I know we're on schedule here -- in short, we ask the sponsors to define the conditioning of their product based off of their expected product's use life. Very simple answer, so we'll ask them, you know, how many days do you plan for your product to be used, and how do you expect to condition that product to emulate that use, and then review what they come back to us with.

DR. HARRIS: Okay. I think -- not that we've resolved all these issues thus far, but could we look at Question 1c?

DR. DURFOR: Level of evidence: If not, on what endpoints should studies be based? For example, for clinical studies, what endpoints are appropriate (partial or complete wound healing; amputation rate; patient-reported outcome measures; local or systemic toxicity)?

DR. SOOD: Thank you. This is Geetika Sood. I just would like to propose two, to start with, one being healing. I think that actually is a good endpoint because that is what we're hoping to achieve with dressings and with wounds. But also, as a second outcome, the avoidance of systemic antibiotic therapy maybe in 30 days after a particular start point, I think that also is a relevant and potentially important endpoint.

DR. ALAM: I think some other relevant endpoints might be pain reduction, because these can be very uncomfortable wounds sometimes, days to re-epithelialization, because even if the wound doesn't enlarge, just managing it over time is very difficult for patients, and I think that leads to the idea of patient-reported outcome measures.

These wounds, there are some deadly chronic wounds, but many of these are not deadly, and chronic and acute wounds can be merely troublesome. So it's relevant, I think, to involve patients in assessing the patient-reported burden of disease.

Finally, as a dermatologist, I would say local toxicity is generally not very important. And the reason I say that is because while some of these substances can elicit a local contact dermatitis or other similar reaction, so can about 75% of the products you buy at Walgreens. So I think that would -- topical irritation is so very common from so many things we use on a daily basis that I think that would not be a reason to not use these products.

DR. SAYEED: I just want to follow that up. Occupational medicine is my primary specialty. We do toxicology. When you sensitize the body to whatever the allergen is, or

the antigen is, you can get systemic effects subsequently. And so if you, you know, expose somebody to isocyanate, for example, then you're sensitized to that, along the lines, and so forth. So I think that local toxicology is actually important.

DR. ALAM: Yeah. I would disagree with that thing.

MS. LOTT: I would just like to point out that the FDA clarified repeatedly, from several different people within the FDA, that these products were indicated for the management of the wound environment and not the treatment of the wound. So if they're not indicated for the treatment of the wound itself, is wound healing an appropriate endpoint, of itself, for the effectiveness of the clinical trial? If that's not the -- again, because FDA has clarified that's not the indication of the wound dressing with the antimicrobial agent.

DR. BURKE: I was just going to say the indication for these wound dressings is to protect the bandage from infection and, by extension, to protect the wound from infection. So I think the endpoint should be that -- I just echo what you say. These aren't to treat -- I mean, everything is to treat the wound, but I think the endpoint should be first culturing every wound, which is not our standard of care necessarily, and then seeing how many wounds become infected after use of these protected bandages.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: I would just echo, from a healing standpoint, that's not why I use these products in wound care. If it heals with the product on, I don't think that was my main end. That's just a nicety. What I'm trying to do is clean that wound up to make the environment better to where it can heal. Or I can get them ready to go to surgery, because from a surgeon's standpoint, nothing cures better than cold steel, but that goes to another end.

DR. HARRIS: Dr. Miller.

DR. MILLER: I think an important endpoint on these things is odor. I think when I -- the most common reason I use a wound dressing like this is because the wound has an obnoxious odor.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Jimmy Holmes. Just for clarification, what was the Panel vote on 1b? Because if we had the answer to 1b, then we know where to go with 1c, and we may not end up down this rabbit hole of chasing clinical studies for devices that are not indicated for those clinical reasons.

DR. HUNT: One of the points I wanted to make is if, you know, some of the data that we looked at today was wound healing and consensus guidelines about whether these should be used, and it's not clear what all of the endpoints were in developments of those consensus. So I think it's really challenging. But if you look at the endpoints for the four things that we were asked to look at, those again are largely based on in vitro or preclinical testing, which should be available and adequate, and that's what the FDA reviews.

If we decide that, you know, every wound is the same, then you can use an endpoint like partial or complete wound healing and do a randomized controlled trial, where you have to stratify based on the patient risk factors. But we all know that these wounds are so different, which is why I like how it was categorized in some of the clinical data that was presented, because some of these are wounds that are going to be there for many years that are not going to be healed. And so using partial or complete wound healing is not going to be an appropriate endpoint.

And same thing with amputation rate; it depends on the type of patient, the risk factors that they have, and the different types of wounds. So, as long as we keep categorizing all wounds sort of all together, we won't make any significant progress.

DR. HARRIS: Dr. Patel.

DR. PATEL: Not sure -- oh, Jean Patel. So one of the indications is preventing external contamination, and it's clear that antimicrobials are being added to these products to prevent bacterial contamination, and that is related to wound healing and preventing infections, which I think are two appropriate endpoints.

DR. HARRIS: So at this time, we would ideally be preparing to take a break. But first we'd provide Dr. Ashar with a summary, or I would provide her with one. And frankly, that's a little difficult to do. So what I'd like to do instead is go ahead and proceed with our break, during which time I will try and, as best possible, summarize our previous discussion, and then we can review that summary when we return from the break and provide that with you.

DR. ASHAR: Thank you, Dr. Harris.

DR. HARRIS: So we're going to take a 10-minute break. Come back around 3:10.

(Off the record at 3:00 p.m.)

(On the record at 3:11 p.m.)

DR. HARRIS: So we're going to not take these questions in direct order. And instead, rather than even finishing the subparts of Question 1, I'd like to go to Question 5.

DR. DURFOR: Sorry. Right. Question 5, Claims and Level of Evidence. For each of the claims cited below, please discuss:

a. Does it represent a clinically meaningful benefit to patient?

b. If so, what type of data should be provided to support the claim?

c. Does it matter which type of wound dressing (solid or gel/cream/ointment or wound wash/irrigation)?

And the claims we wish for you to comment on are:

- Maintains a moist wound environment;
- Covers and protects the wound;

- Provides a barrier to penetration of microbes to the wound, which may reduce the risk of infection;
- To enhance the microbial barrier function and minimize growth of microbes in the wound dressing;
- An antimicrobial effect to minimize microbial contamination/colonization of the dressing;
- Intended for use up to X -- some defined number of days;
- A non-adherent layer reduces pain during dressing change;
- Maintains low bioburden during shelf-life storage and after repeated openings of the package;
- Relieves the symptoms of skin irritation, such as itching and burning;
- Irrigation loosens and removes debris, exudate, and infectious materials from the wound.

Thank you.

DR. HARRIS: So we've been discussing, in indirect ways, some of this already. But I think these are obviously claims that FDA would like our opinion and discussion on, regarding, as was stated, are these claims clinically important? What sort of data would we want to see to validate the accuracy of these claims? And then, is it specific to a particular type of wound dressing?

So I'll open it up for some discussion and comment, starting with "Maintains a moist wound environment."

DR. ALAM: I think that is a clinically meaningful benefit to the patient. Are we just doing (a) right now?

DR. HARRIS: You can do (a), (b), and (c).

DR. ALAM: Okay. I think, too, in terms of what type of data would be provided to

support the claim, I think it could be in vitro or in vivo. This is something that I think is not something that necessarily needs to be performed on a patient in a clinical trial, that any reasonable laboratory or clinical data even outside of trial would be sufficient.

And (c), does it matter which types of wound dressing? I think the same rules would apply if any of those dressing types wanted that sort of claim.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Thank you. I would agree with Dr. Alam, that maintaining a moist wound environment is a clinically meaningful benefit to the patient. And I think, at most, the type of data to support the claim would require animal model testing. I don't think it needs to be done in patients. And it does matter which type of dressing because I'm not sure how wound wash/irrigations would maintain a moist environment since they just are squirted on and run off. So I don't know that that claim could be applied by the washes.

DR. HARRIS: And do you have any comments about what would you be looking for in your animal trial to determine maintenance of a moist wound environment?

DR. HOLMES: Well, I mean, you could measure humidity under the dressing in a pig model.

DR. HARRIS: Any other -- Dr. Wolf.

DR. WOLF: So I think the key variable missing here is time. You know, what are we talking about? Maintains a moist wound environment over what period of time? And a wash is going to do that, optimally, would be the best one, for about 20 seconds. Right? And but after that, you know, it's going to, you know, first order decay right after that, and whereas a solid one that is, itself, you know, like a gel or something like that that's in a solid thing, you would expect it would have been longer. So I think it would have to do with what the manufacturer was claiming. And a solution here might be a moist wound environment for how long?

DR. HARRIS: Any other discussion? So it sounds like everyone agrees that maintaining a moist wound environment is important for the patients' wound care. It sounds like there is some debate as to whether that can be effectively done with a wash as opposed to a gel, an ointment, or a solid dressing that had some sort of moisture-containing component.

Unclear exactly what would be the best clinical study or preclinical study to be done, but it seems like people would be comfortable with an animal study as opposed to a clinical trial to demonstrate moisture efficacy, and some might even be comfortable with in vitro testing.

DR. CALIFF: I just want to make sure I understand this correctly. So the outcome would be humidity measurement and over some period of time? And everyone agrees that that's the right thing to measure?

DR. HARRIS: Well, I don't -- go ahead.

DR. HOLMES: I mean, other things you could measure would be water content of the dressing. I mean, there are a bunch of things that would reflect moisture in the wound. It doesn't require a human.

DR. CALIFF: And is there a right amount? Or is the more, the better?

DR. HICKERSON: Well, that goes back to your home. What's the correct humidity in the walls or the water content that you want in your drywall or the lumber that you're going to use to build your addition to your house with?

I've got just a device that I stick in my drywall, or my wood, to see what it is. And in this case, if in the house it's less than 18%, it's usually considered to be passable. If you're going to buy a new house, and particularly, you look at it in a situation like Memphis, Tennessee, on the Mississippi, we have some problems. Same thing exists, though, with your dressings. I mean, I have to look at my dressings more frequently than what you're

going to have to look at in Phoenix.

So it varies. So that's where the instructions for use may also come into play, rather than just across the board.

DR. HARRIS: I think part of the question that I'm hearing, though, and just to be -- not to be contrarian, but I think we've all witnessed an evolution in the assigned importance of keeping the wound moist. And I guess the question is do we know how moist and for how long, is part of what's being addressed.

And while we're not building a home, I think the question is do we feel we need to have more specific evidence regarding not just is the wound moist but how moist?

DR. CALIFF: Let me just point out that what -- is ideal to be addressed, in general, through a well-done registry. So if this is an important thing for patients, to have a moist wound, and we don't know the right amount for different kinds of patients, if you have a registry, and you measure moisture and wound healing, independent of intervention, you could -- and I'm sort of asking. It sounds like we don't know the answer to this question.

DR. HICKERSON: You're correct.

(Laughter.)

DR. HARRIS: Ms. De Luca?

MS. DE LUCA: If the wound is dry, and I have to go to a doctor and take a whole afternoon of waiting for my turn to have it scraped off and then go home and be in pain, more moisture on it, I'd have say moist.

DR. HARRIS: Okay.

MS. DE LUCA: How dry can it get before -- you know, like Arizona?

DR. MILLER: It's really a different question. I mean, does the wound dressing keep it moist? That's pretty answerable. Well, how moist should it be? That's a completely different question and one that would require a whole different set of studies, and it would

depend on the wound and the patient and the etiology.

A radiated wound's going to be different than an infected, contaminated wound, or a burn wound that's leaking, you know, material all the time. So the question of does the dressing maintain a moist wound environment, I think that's pretty answerable.

DR. HARRIS: But this is within the context of does it represent a clinically meaningful benefit to the patient. So whether it's wet or not is necessarily a binary response. Officially, I think they're asking us, do we think that's clinically important, and if so, based upon what evidence?

DR. MILLER: Well, I guess a better way to say that would be does it prevent desiccation, because desiccation is clearly bad. There's no question about that. You know, how wet should it be? I don't know if anyone knows the answer to that.

DR. HARRIS: Yes?

DR. BURKE: I just wanted to exactly add that, that we all know desiccation is bad, and we know that some degree of moisture is good. But there was a syndrome of our soldiers in Vietnam that had foot immersion syndrome, and literally, because they were wearing shoes in the swamps, their feet were very injured, and they were injured and not able to even walk for sometimes weeks after they had this foot immersion syndrome.

So the question is how moist? And I don't know the quantitative number, but I'm sure that must be somewhere in the literature. We don't think it's in the literature.

DR. ELAM: But to, I think, answer the question perhaps that the Commissioner raised, I do think, at least within dermatology, and I suspect in some other disciplines and some other contexts as well, there is an agreement that moisture is a good idea. And, in fact, that's what we routinely do; we emolliate healing wounds to some extent, while the exact amount hasn't been determined for particular patients.

DR. HARRIS: Okay. No more discussion on that topic. The second claim is "Covers

and protects the wound." Is that clinically meaningful? What sort of data do we need, and is that something that all of these dressings can do, or these products?

DR. SOOD: Thank you. I do think that is clinically meaningful, particularly for surgical site infections. If you have lumbar fusions or different locations of these dressings, they are more likely to peel off or not really remain the way that they are supposed to. And in certain situations where patients may get those areas wet, that could become very significant. So I think that to measure that, you actually would need a little bit of clinical data to see how it actually performs mechanically.

DR. HOLMES: Jimmy Holmes. In all honesty, I mean, this one is a given. I mean, if we didn't think it was going to cover and protect the wound, we wouldn't put it on there. And I mean, for that really to be claim borders on absurd. But it's definitely clinically meaningful and beneficial to the patient. And it can be tested in innumerable ways again, and it doesn't require humans. I mean, it could be done with registry data. I mean, what patients come back with dressing intact, which ones don't? You could do it with animal models. And again, I don't think it applies to the wash and irrigations, but it does to the other two.

DR. WOLF: So in my experience in running a burn unit, the wound care techs, all of our wound care techs come up with these ingenious ways to try to keep wounds, you know, dressings on patients, right, and to cover and protect the wound. Any dressing can cover and protect the wound if you have a clever person, you know, using all kinds of fancy devices to try to keep it on.

But what I think matters is what the patient thinks covers and protects their wound, right, in that, you know, we staple things to people and all these other things. And then patients may complain about that. They'll complain about their dressing rolling down or whatever, this other things. And so I think the real clinically meaningful benefit, in terms of

a device covering a wound, is whether the patient thinks it covers the wound and what they have to do to keep it there.

DR. HARRIS: And I think I'm hearing, from your comments, Dr. Holmes, that you feel that could be equivalently done by an ointment or a gel. It doesn't necessarily have to be a physical, mechanical dressing.

DR. HOLMES: Correct.

DR. HARRIS: Okay.

DR. HOLMES: Yes.

DR. HARRIS: Any other comments? Oh, yes.

DR. BURKE: Well, just, again, it's obvious, but obviously you need a physical cover over parts of friction, if someone's wearing a belt over a wound or other articles of clothing, or on the feet particularly, you need padding and covering. So it really depends on the part of the body, also.

DR. HARRIS: Okay. The third claim is "Provides a barrier to penetration of microbes to the wound, which may reduce the risk of infection." Someone like to address whether they feel that's clinically meaningful, what type of data they'd like to see to support that claim, and does it matter what type of material is being used?

DR. ALAM: I think that, again, like the previous claim, it's really intrinsic to the materials themselves and to their approval. And so I would say yes, it does represent a clinically meaningful benefit. And in terms of the data, the in vitro data pertaining to whether or not the material is penetrated by microbes, by specific kinds of organisms that FDA has determined are appropriate to test, I think, would be sufficient because the claim goes on to say, this may reduce the risk of infection.

So it doesn't necessarily suggest that some preexisting infection would be mitigated by this. But it seems like the barrier would merely prevent external microbes from

penetrating into the wound, which might be able to be shown by showing the integrity of the material overlying the wound.

And regarding the type of wound dressing, I would suspect a solid or gel/cream would probably be more useful, like Dr. Holmes had mentioned earlier, as versus something that was applied and then was removed by irrigation.

DR. HARRIS: Dr. Sood?

DR. SOOD: Thank you. I may be the minority opinion here, but I think that this is not something that we can say is necessarily the case. We don't know -- having an interest in the microbiome of the wound, I don't think we know if using antimicrobial agents or other things that actually kill off the good bacteria is going to help or hurt wound healing. So I think that there's more complexity to that indication than simply we can assume that it's going to reduce infection.

MS. LEACH: One of the complexities was on, I thought, if you have your entire stomach area covered, one area is going to be popped off the body way ahead of its time, and what do you do? Do you have to then go back and rip the whole thing off and start again? Yes, you do. But we have to consider that a lot of -- and I'm sure it's true with back wounds as well.

DR. HARRIS: Commissioner?

DR. CALIFF: This is a question for my CDRH colleagues. The thing that bothers me is they may reduce the risk of infection. Well, you know, I might be able to fly to the moon tomorrow, but this doesn't seem like the typical thing I would think of as a claim because it either does or it doesn't. And if you claim that it does, you should show that it does. So does CDRH allow claims for might or possibly could or maybe, you know, if we were lucky, this would happen? I'm not understanding that.

DR. ASHAR: I have to say that these claims were taken out of FRO products in

general. So these claims exist in the marketplace. Now, whether they are actually in the indications for use or whether they have evolved to be in the labeling, they nonetheless are present. The spirit of our review is focusing on the dressings themselves in reducing the colony count or the bacterial load on the dressing themselves.

And in, you know -- I can't tell you, and perhaps Dr. Durfor can comment on this, as to whether or not there was any sort of justification along these lines historically. But many of these claims have seeped into the labeling on a historical basis.

DR. DURFOR: Yeah. I'm not sure -- Charles Durfor. I'm not sure I can give you the history of this. I would suggest that the cusp of this question is we do the testing that Mr. Kitchel has showed us, and the products can function as a barrier in vitro. And so the question now to discuss, I think is, is the clinical benefit with it. That's the second half. If it's not, or if it is, then what data are necessary?

So I think it's two parts. One is can the product be a barrier. The other half is, is that barrier reasonably believed to have clinical benefit to the patient.

DR. ELMORE: Susan Elmore. So I do think that this question can be answered with animal studies. And hopefully we'll get to that discussion later. Is that right? Okay. So I was just waiting for that discussion.

DR. ALAM: And I'd read -- Murad Alam. I'd read this claim to really be the first part, where the claim is "Provides a barrier to penetration of microbes to the wound," and then the "which may reduce" is really a parenthetical, which I suspect, if I may just speculate, might have been someone wanting to say it does reduce, and then FDA maybe saying you can't say that in the absence of any evidence. But I think that's really a parenthetical. But perhaps it should be a separate claim.

But if it were a separate claim, then again, we might be going outside the purview of the materials as they're currently approved, where they're not being approved for any

specific impact on the skin. They're just really being approved for their own intrinsic function, if my understanding is correct.

MS. LOTT: Right. And I think we're not here to defend, you know, what these claims are or are not. What we'd like to understand is what you think these mean. And if it is of no meaning to you, then perhaps it should be stricken.

DR. ALAM: I would say that it, the latter, the parenthetical is probably not of much meaning, as the Commissioner has noted, and probably a little confusing for patients.

DR. HARRIS: Dr. Wolf.

DR. WOLF: This one can't be done in people. The only way you can truly demonstrate that it is a barrier to penetration is if you sample the whole wound, which will induce harm to the patient, and you can't do it. So this one can only be answered in a preclinical model.

And I agree with Dr. Califf. What is may, might, could, would? And that should just be stricken.

MS. LOTT: But to your point, this is directly related to claims 3 and 4, that you specifically said could only be answered by clinical studies just a second ago.

DR. WOLF: I didn't say that. I said that you have to test it in people and to see the effect that you want to see. In this one, you can't test whether they have penetration of microbes in the wound without actually excising the wound and sampling it. You can do biopsies or something like that, and that's going to be subject to sampling error, and I wouldn't believe you if you tried to publish it in my journal.

MS. LOTT: Well, I'm just saying, to me, those two statements sounded contradictory, just for the record.

DR. HARRIS: Dr. Miller.

DR. MILLER: Yes, thank you. This, number 3 seems related to the fourth one down

here, and really, provides a barrier to penetration, you could say that of any dressing, with or without the antimicrobial. But whether it's an enhanced barrier, now that's something which needs to be demonstrated and is not necessarily the case, you know, because I don't know if a dressing with an antimicrobial in it is going to increase the barrier from the outside world to the wound over just a simple dressing, you know. So if I could jump to that one as they're kind of related.

DR. HARRIS: Dr. Hunt?

DR. HUNT: Yeah, so I was going to say, 2, 3, 4, and 5 are really all related because you're talking about protecting the wound from what? Are you talking about protecting from some mechanical injury, the clothing the patient's wearing, shoes or whatever? But then, what might be -- that's one meaningful endpoint, but the other one is to prevent a barrier to microbial infiltration and minimizing that. So all of those are really related.

DR. HARRIS: Dr. Alam?

DR. ALAM: Are we doing 4?

DR. HARRIS: If you'd like to be, sure.

DR. ALAM: Yeah, with regard to the fourth claim, I think the word "enhance" is problematic, just from a semantic standpoint, because as other speakers have made it clear, it's not clear whether that's in comparison to some other dressing or to nothing at all. So it could possibly be removed. You could just say to create or to form a microbial barrier without using the word "enhanced," which is confusing.

DR. HARRIS: So I guess part of what I'd like to hear some additional comments on is when you think about this dressing or this gel or ointment as a barrier, and having an antimicrobial property, are you thinking of that as something that's actually going to be preventative for the patient, therapeutic for the patient, or simply protect the actual substance itself from becoming colonized or contaminated?

DR. HOLMES: Well, in light of the options given, and what we're being asked to address, I would say, from my perspective, it is protection of the dressing material itself. I mean, we're not being asked to take the step, at this time, towards anything further. And, you know, an addition of an antimicrobial to either the gels or the solid dressings, claims 2, 3, 4, and 5, just as Dr. Hunt said, I mean, all are getting at the same thing. And they can all be answered appropriately with an animal model.

And I mean, as Steve pointed out, a lot of it you can't do in a human because you're going to have to expose them to added risk and potential harm.

DR. HARRIS: So is that the same to say that you feel they need to be demonstrated in an animal model before that claim should be associated with that product?

DR. HOLMES: Yes.

DR. HARRIS: Dr. Reller.

DR. RELLER: On these three components, I do not think that one can extrapolate from animals to humans. If one has a warm, moist -- and we all think moisture is good or at least desiccation is bad -- a warm, moist surface contiguous with skin flora or skin microbiome, whatever term one wants to use, it's impossible -- I mean, it will be -- you can use the word "colonized." There will be organisms there. That's not the point because all the organisms are not the same in terms of their potential effect on wound healing and the implications for spread to the patient.

You know, in some ways, a dressing that has a high microbial burden, I mean, to me, it's like analogous to why the foremost -- if there is tissue into which antimicrobials can't penetrate, because this is therapeutically, can't penetrate, because they're devascularized, the treatment is primarily debridement. Everyone that's around this table recognizes that.

To me, if there's a high microbial, as a moist, soppy, smelly dressing, the debridement is to remove the thing and replace it, and if further debridement is -- so I think

that if one is going to take the primary mode of action concept and that there is the covering, the dressing that people in general think is wise, good, prudent, aesthetically pleasing, patients like, etc., to me it's a whole another matter of extending through surrogacy or animal models or anything else that somehow the addition of a specific antimicrobial agent adds anything to that covering or primary mode of action, and if what is really effective is the drug, then it becomes a drug. That is an antimicrobial.

And I realize that all antimicrobial agents are not necessarily the same. There's been some obfuscation of antibiotic and antimicrobial agent. I think what we're really talking about is if an antimicrobial agent is used therapeutically, is its presence as an aspect or an integral part of these dressings, does it add anything? And I don't think that can be got at, apart from a controlled clinical trial.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: Dr. Harris, just to follow up on your question on whether or not these dressings are used for treatment, everyone on the Panel is an expert. And so I'm sure you're using things appropriately. But in the community hospitals and in private practice, among nurses, among other healthcare providers that aren't experts, are they using these dressings as treatment? And my thought is yes.

DR. HARRIS: Well, I'm personally willing to have my expertise challenged. I actually don't know that we can assume that everyone is using these dressings, despite your experience level, because I don't know that we have all the information necessary to make, you know, evidence-based decisions. But I think your point's well taken.

Dr. Campbell, then Dr. Hickerson.

DR. CAMPBELL: Hi. Greg Campbell. So I'm a statistician, and I've been pretty quiet because I don't really feel I can weigh much on terms of the clinical aspects. And so for number 5, though, for claim number 5, I'm not going to touch the clinical meaningful

benefit of it, but it strikes me that if you're asking does the addition of a microbial to the barrier help in terms of minimizing the growth of microbes, that calls, I think, for an experiment. And I would hope that we would think about this quantitatively.

And one of the reasons for doing that is if you can figure out how much of an advantage the antimicrobial would be, that would be helpful in terms of the benefit/risk and the more global risk at the societal level of antimicrobial risk. So I think, in that case, it makes sense to think about that in that way.

And I actually agree with Dr. Reller that it might make sense to think about a clinical trial for this particular number 5.

DR. HICKERSON: But then in our packet, we also see the studies that were done that show where the microbes were actually trapped within the dressing. And so therefore, I would go the opposite of what Dr. Reller has suggested that we would have to do because of that.

DR. ELMORE: Susan Elmore. I agree that humans are certainly the best model. But I think we've heard a lot of discussion here today that the human condition is really quite variable in terms of the types of wounds, prior treatments, bacterial burden, type of infections, etc. So comparisons between humans can be really challenging.

On the other hand, I think that animal models can really be a component of the valid scientific evidence that people are looking for here, and particularly with respect to manufacturers' claims. They would not be appropriate to address things like the shelf life or the sterility of a product, nor could they address, you know, antimicrobial resistance. But I think that, in terms of prevention of contamination of the dressing by external bacteria and providing a barrier against microbial entry into a wound, animal models can address those two things. There are published animal models for various types of wounds, and those rodent models could easily be adapted to evaluate these devices and those questions.

And so, you know, I think you'd have to look at the effectiveness of antimicrobial-infused products versus those with no antimicrobials. That would be important. And also, various wound types and various microbe exposures, they could all be done in the lab on an animal model. And other effects of the devices, such as sensitization, delayed wound healing, moist wound environment, all of those can be evaluated in an animal model as well.

But, of course, you know, human are the best models, but they're not pathogen-free. Their environment isn't pathogen-free. They can have confounding medical issues, varied immunological health status. So understanding the limits of the study would be critical, and importantly, this is what we always say with animal studies, is that the results would have to be interpreted based on the specific conditions of that study. But I do think that animal models could really add to the scientific evidence here.

DR. HARRIS: Dr. Hunt, then Dr. Reller, then Dr. Wolf.

DR. HUNT: So one other thing to -- I really like that discussion about animal models. And looking at the specific variables that we're talking about are very important, reducing infection and so forth. But again, we have to look at other clinically meaningful endpoints with the patients. So if using these types of dressings can help reduce the number of times a dressing has to be changed, and the bacterial load that accumulates during that time between dressing changes and so forth, that can be a very clinically meaningful endpoint to the patient as well.

So when these claims are talking about minimizing growth of microbes, that may not necessarily translate into reduced infection of the wound per se, but it may mean that the patient can go with two dressing changes a day or one a day, rather than having to do it four or five times a day, which can be a significant quality of life issue.

DR. RELLER: Barth Reller. If one conceives of these dressings as barriers, traps,

presumably that's good because the organisms that are going to be replicating in a warm, moist, nutritious environment in the dressing before it's removed, if, in fact, the dressing does function in that way, I could not -- and this is anticipating some of the following questions -- I could not imagine a better milieu in which to encourage the emergence of resistance than such a dressing, trap, sop, whatever you call it, with a antimicrobial agent used for human or veterinary use being incorporated into the dressing.

I mean, it becomes a risky milieu.

DR. WOLF: So for the record, I just want to point -- so we talked about 2, 3, 4, and 5 being the same thing. They're not. Coverage and protection of the wound is from protection from the exterior environment, and whether that be air, dry air, the wall, the bed, the chair, all these other things which have nothing at all, nothing to do with microbes or have very little to do with microbes; 3, 4, and 5 are all about microbes, which is also related, but it's not the same thing. And I think the one in the middle, where we start talking about penetration of microbes to the wound, that is, by definition, going to require sampling of the wound, not the dressing, whereas 4 and 5 are just the dressing. So that could easily be done clinically or the bench, either one. And I think they're probably equivalent. But I personally would prefer the human, as you guys know.

But for the third one, that one's different. That's going to require sampling of the wound itself, which can cause harm to people.

DR. ALAM: I think one thing that we haven't discussed much, in terms of what kind of a study might be appropriate and what type of data might be sufficient, is the risk inherent in the use of these combination products. I think the idea of cardiological products was brought up before, and stents and so forth. And I don't know anything about cardiology, quite frankly, but I would suspect if something goes horribly wrong with a stent, someone could die relatively quickly, whereas if something goes wrong with the adhesive in

one of these devices, it could fall off. And then it could be reapplied or not reapplied or a different product could be used.

So while I would certainly be very eager to suggest that most claims be tested by an RCT or a clinical trial for something that had potential catastrophic outcomes, I think some of these other claims about barrier might be okay to test in vitro.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Jimmy Holmes. Dr. Reller brings up a very good point that gets to the antimicrobial resistance issue. And, you know, the Agency may want to start thinking about some of these topical agents from the standpoint of what's bacteriostatic and what's bactericidal because it will make a huge difference in that milieu Dr. Reller's worried about as to whether something's cidal or static and whether it maintains the claimed levels to achieve the cidal or static mechanism. And I would put forth that, I mean, bactericidal agents and static agents are very different animals.

DR. CALIFF: Just to have the fun of making it even more complicated, if people are interested, Question 3 gets at this, too, but I think it's embedded in here, and it's been a topic of discussion. Is it simply the counts of bacteria that matter? You know, I'm far from an expert, but I've learned in my current job that plasmids are tricky devils. They're promiscuous, they jump from thing to thing, and it may be you could have a lower bacteria count but actually have a much higher risk of conversion to an antibiotic-resistant infection, which, I think, is what Dr. Reller was getting at.

In other words, as we're understanding resistance better, this is not a matter of just, well, as we can do sequencing now, we can actually see things we couldn't see before. And the constituents, constituency of the bacteria may be more important than the absolute count. I'm not sure we know. Maybe you guys have looked into this or thought about it.

DR. HARRIS: Dr. Miller.

DR. MILLER: I think, when I think about the clinical question about this, there's really three areas of concern. One is does the wound heal? That's the ultimate -- I mean, that's got to be a goal here. The second one is the infection rate. And that's a clinically relevant question. And the third is the management piece. I mean, how often are the dressings changed? How badly does the wound smell? And these don't necessarily affect the healing or the infection rate, but they're real, genuine management issues for the patient.

I think, you know, when I see 700 products, the first thing that comes to my mind is none of them really work very well, you know. So I mean, so if there's so many out there, you know, then, you know, I think that they probably don't make any difference whatsoever with healing. And they probably don't make any difference whatsoever with infection either. But the management thing, these endpoints have to be included in assessing their value because I think they do make a difference in these types of issues.

DR. HARRIS: Of course, you wonder if the endpoints are things like odor, there may be other agents that have no effect on the microbiome that could address odor.

DR. MILLER: Well, I agree with that.

DR. HARRIS: Doctor --

DR. PATEL: Yes, Jean Patel. I wanted to weigh in on the static versus bactericidal issue and the propensity for selecting for resistance. So I think there's no correlation between whether an antibiotic is bactericidal or bacteriostatic and its ability to select for resistance. I think it's more closely linked to the mechanism of resistance. So, for example, fluoroquinolones are cidal agents that require a single base pair change in a bacteria for resistance to occur. And so that's a type of resistance that occurs very readily, whereas other antibiotic agents may require acquisition of a new genetic element that's very uncommon, and so you'd see less resistance.

DR. HARRIS: Dr. Sood.

DR. SOOD: I just wanted to add to the type of bacteria discussion, because as an epidemiologist and hospital epidemiologist, that's a big issue. And as Dr. Califf was saying, certain bacteria and plasmids, like CREs or other plasmids, can be readily transmissible. And I think, to piggyback on Dr. Reller's point, having a sub-therapeutic level of antimicrobial and having proliferation of the bacteria is a setup for resistance mechanisms which can cross species, if they happen to be plasmid-mediated.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: So two questions along those lines would be, number one, does the amount of silver in the dressing, say, for silver products, matter? Because we've gone to the extent that even some of the over-the-counter products that you could get with a band-aid had silver on it, but my concern was that that was such a small amount, we were going to get into trouble.

But on the other hand, those that we use from the burn standpoint have quite a bit of silver. And then looking at that product over the millenniums that have been utilized, would it indicate that the resistance that develops to silver, number one, is there any clinically significant known resistance at this point? And number two, the way that it works, in about four different methods, help prevent that?

DR. HARRIS: Dr. Patel.

DR. PATEL: I think those are tough questions to answer. I think the rates of heavy metal resistance to bacteria are not well studied, and so we don't have good information on the number of bacteria that have resistance or the amount of the silver that's required to select for resistance.

DR. HARRIS: I'd like -- oh, Commissioner.

DR. CALIFF: It sounds like great news for those interested in research in wound care. There's a lot of opportunity for learning here.

DR. HARRIS: So I'd just like to broaden our discussion to include questions of "intended use for up to X number of days" and/or "a non-adherent layer reduces pain during dressing changes."

DR. CALIFF: Sorry, I can't resist. I mean, reducing pain, that is such an easy clinical trial to do. I could probably just do it at the FDA as I walked around and talked to people that had --

(Laughter.)

DR. CALIFF: So that seems, you know, very straightforward. The dressing change, I did want to raise this in relation to several of these points. I don't know, when I used to run intensive care units, which was a few years ago, one of my biggest worries was people getting complacent with wounds sitting underneath dressings for days at a time. And I used to make people take the dressing off to see what was under there.

So to me, it's come up several times with regard to other endpoints, where it's not all or none, and it's not just a linear scale where more is better or less is better. There's probably some optimal point, which is different for different kinds of people. But, you know, I wonder about the wisdom of a blanket indication for covering up a wound for X number of days, whether that's necessarily a good thing as an indication.

DR. WOLF: It is for your patient, right. Because every time you change a dressing, it hurts. And so, like in a burn unit, you know, that's all we do is wounds, right. And so we're acutely aware that every day -- every patient is examined twice a day, even if a dressing is in place, that we intend for it to stay X number of days. And --

DR. CALIFF: Good luck.

DR. WOLF: Right. But we inspect the wound, say, you know, does this look like it's supposed to look at day 3, or whatever it is. And so we are inspecting the wounds; we're just not changing the dressing is the way I would put that, from a clinical perspective.

MS. LOTT: So just from a regulatory perspective, knowing what goes into submissions, a lot of claims like this end up being related to the biocompatibility data the company may have on the device. For instance, they might not have chosen to invest in biocompatibility data that says it's okay to leave the wound on place for 30 days or whatever, as opposed to, you know, 5 days, 1 day, you know, less than 24 hours. It may be related to performance data, not just to what they intend for it to be used on the wound for.

DR. ALAM: I think, with regard to this claim, I would agree with previous commenters -- it's Murad Alam -- that the intended for use for up to X number of days, it's uncertain whether this represents a clinically meaningful benefit to the patient. And I think that probably derives from the fact that's been raised by others already that the wounds we are discussing are really a heterogeneous group of wounds, so perhaps for burn patients it's a really bad idea. But for some of the minimally acute post-surgical wounds that I see, it probably doesn't make that much difference. So I suspect it would probably depend on the kind of wound.

As to what kind of data should be provided, I suspect that probably would need some clinical data. How else would we know if you could apply it on a patient for a certain number of days? I suspect in vitro or maybe animal study data would be enough, but some kind of data on some living organism probably would be necessary.

And as to the (c), what type of wound dressing, I guess that goes to the wording itself, intended for up to X number of days. It's not clear to me if that means one application for X number of days, or whether that substance itself should only be used in total for a certain number of days. So I think there's some ambiguity there, too, as to a particular item or the product in general.

DR. HARRIS: Dr. Hunt.

DR. HUNT: So this is another area where, like you mentioned, heterogeneity of wounds is important, because if you're talking about a dressing over a central venous catheter, that's something that you don't want to inspect every day. And that puts the patient at risk for bloodborne infection. So if you can have dressings that can be applied for a specific period of time, and they don't have to be changed, and they don't have to be examined, then that's important.

And same thing with wounds from catheters that we place at surgery, where having to change those dressings every day or multiple times during the day is probably unnecessary for the patient, but it's something that's always been done. And if you can have dressings that are applied, which there are some now available, that can be in place for a certain number of days, then that's a significant improvement in quality of life, may reduce infection, which can reduce the time that patient gets to adjuvant therapy after surgery. So again, it depends on the type of wound that you're trying to cover.

DR. CALIFF: Would you be happy with just biocompatibility data, or would you want clinical data to make that determination?

DR. HUNT: So in that case, I think you have to have clinical data. I think you have to have -- and with catheter, central venous catheters, there are plenty of studies that have been done that can be recapitulated for other types of wounds to get that information.

DR. SOOD: I would just add that for the central line data, and actually even for post-surgical wounds for us, that that is related to the actual contamination, we think, that people aren't using proper hand hygiene, and the more you're changing the dressing, the contamination becomes more of an issue. So I'm not sure what this question is specifically meant to address. Is it the related factors, like the contamination involved, or just specifically about the dressing itself?

DR. HARRIS: Dr. Holmes and Dr. Hickerson.

DR. HOLMES: From my perspective, this is another one that would be quite amenable to answering the question in an animal model because you could control for the amount of exudate that the dressing is exposed to. And, you know, I mean, that's going to have a direct effect on the antimicrobial concentration, etc. And you could literally control for that much better, because like with the central line dressings, I mean, central lines stay dry, ideally, except in our burn patients, when we don't have any dressings on them, and we just cross our fingers a lot of times and cover them with whatever we got.

But, you know, you could really control the wound exudate. You could even control the contamination parameters surrounding a wound if you did it in an animal model, and it would tell you how long that given dressing maintains its antimicrobial activity with respect to the indications for it.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Thank you, sir.

I was always under the impression that it was the amount of the heavy metal that was in that dressing, that it would be able to be available. So, therefore, like Dr. Holmes says, I think that an animal model would suffice for those type of studies.

DR. ASHAR: I just had one thing I wanted to point out. For purposes of this question, we took these claims and kind of put them all separately, but as you saw in some of the presentations, the manufacturers oftentimes link them together. So "intended for use up to X number of days," for example, "to enhance the microbial barrier function and minimize growth of microbes in the wound dressing" could be strung together. So please also consider that as you're providing feedback to us.

DR. MILLER: Now, I think a claim like this has to be accompanied with an indication, because, you know, the number of days that it can be efficacious will depend on the rate of ongoing contamination by the source of the bacteria. So if it's a really bad wound, say a

fistula of some kind or something, you'll probably have to change it every few hours. But if it's a central line wound, the contamination rate is extremely low, and you could maybe put a date on that, so --

DR. HARRIS: I mean, it would seem to me that that sort of a statement has to speak to an intrinsic property of the device and not be specific to a patient. In other words, you know, how would you -- I mean, all fistulas aren't the same, and so to say that this can be used in fistulas for up to 7 days, I mean, it seems like it has to be more about a question of what's in the dressing itself, and how that is going to be exhausted or somehow ineffective after a prescribed period of time or cannot be reliably effective after a prescribed period of time?

Dr. Hickerson.

DR. HICKERSON: And also, it seems like that there's instructions for use with each of these products. So I think that that has to be taken into consideration, how that's described for the intended use. As patients differ, then that use -- and that's going to be a clinical decision based upon what you've got within your wound bed as well. So I think that it has to go back to the device rather than to the individual patient.

DR. HARRIS: And perhaps we can have a little discussion of "Maintains low bioburden during shelf storage and after repeated openings of the package." This has been discussed a little bit already by Dr. Murad's -- Dr. Alam's comments. And "relieves symptoms of skin irritations, such as itching and burning." Clinically relevant, what type of device?

DR. ALAM: Murad Alam. I think -- yeah, I think reducing itching and burning would be a good, clinically meaningful benefit, assuming, of course, the patient were having such itching and burning before the device were applied. And obviously -- well, maybe not obviously, but I would suspect that the type of data that should be provided to support the

claim would include some clinical data, since an animal would be unable to communicate itching and burning.

As to whether that'd be an RCT or just a cohort study, I think probably the latter would suffice. You know, if a significant number of people got relief from itching and burning, I don't think that if some others didn't, that would necessarily be a problem.

And regarding what type of wound dressing, I suspect, just based on common sense, it's more likely that a dressing that -- well, actually, I don't know. I suspect any of those could possibly reduce itching or burning.

MS. LOTT: So there are several OTC monograph drugs where the indications, it's okay to say, without getting any additional approval or clearance from FDA, that it alleviates itching, burning, irritation. So, you know, what would the expectation of translating that already kind of well-known intended use of that into the wound dressing material?

DR. HARRIS: Dr. Sayeed?

DR. SAYEED: I guess my question would be, does that particular label specify local itching and burning? Is it systemic itching and burning? You know, does the labeling have any more specificity to it than that?

DR. ASHAR: I think, Dr. Marquart, maybe you can comment on what we see in the labeling for that. The other point, while she's coming to the microphone, that I want to raise is that we should be, as you're thinking about this, thinking about benefit/risk as well, with some of these claims, is as sponsors seek to make these claims, we also want to understand some of the risks associated with them because that's going to get into the discussions related to Day 2.

DR. MARQUART: All right. So for the claim relieves symptoms of itching, burning, irritation, we're talking mostly the creams, gels, or ointments, so not the antimicrobial wound dressings. But as I talked about, with atopic dermatitis or radiation dermatitis, so I

know we said this class is very broad. And that specifically, so it's going to be local. You know, the cream is to manage the symptoms of, you know, itching, burning, pain, whatever it is, in that area for that dermatitis.

DR. ALAM: Can you clarify what kinds of data historically manufacturers have had to provide to substantiate that claim? I would suspect if it's atopic dermatitis that's specifically being treated, that's a very direct benefit. Would that have to be a clinical trial or something?

DR. MARQUART: Right. So I can't specifically say, you know, what -- you know, randomized, but from ones that I have evaluated, and then for previous ones that I looked at, there are controlled trials. And a lot of times the control is the cream without that specific ingredient in it. And then the other thing is the product. And so that they're looking at reductions in those symptoms in those patients.

DR. HARRIS: Yes.

MS. LOTT: This also seems to speak to Dr. Wolf's initial points about patient preference. And it seems like that would be a legitimate way to collect some data to validate the efficacy. Does the patient feel that they are less itchy or uncomfortable? Perhaps there are better/worse type of scale or questionnaire.

DR. HARRIS: Any comments regarding "Irrigation loosens and removes debris, exudate, and infectious materials from wound"? So that sounds like that's specifically referring to a wound wash/irrigation solution.

DR. WOLF: So that happens with water, right. And/or water and anything containing water. And so I think that that particular claim is self-evident.

DR. HARRIS: Well, they're not necessarily claiming exclusivity. They're just saying they do it.

Dr. Reller.

DR. RELLER: To follow up on Dr. Wolf's comment, what is listed here is a given, of saline. However, what seems to me the Committee is charged with is whether or not the addition of a specific compound, especially an antimicrobial agent to that saline, has any additional clinical utility. And that is the central -- is there evidence that these additions do anything other than what the dressing, the irrigation solution do in their own right?

DR. HARRIS: So I just want to reiterate that I think what may be very useful to FDA is to hear from the experts, or people with significant clinical experience, what are the factors that are helping you decide, if you're going to irrigate a wound, that you use saline versus water versus some commercial irrigation fluid, for example? Or whether that same question is when do you decide to use a silver-impregnated dressing or one impregnated with chlorhexidine? So I think those are the type of thinking that will help the Agency then identify what would be necessary to verify or validate that indication.

DR. RELLER: Barth Reller. Along those lines, I mean, there's always this benefit versus risk. I would surmise -- this is speculation -- that some of the classifications heretofore, of the combination agents is -- well, we don't know whether they really work, but they're not doing much harm.

Well, there's another corollary -- and I think about the stent, eluting stent analogy, is yes, there can be catastrophic consequences. Therefore, one is willing to incur more risk. But if there's a question about whether there's any benefit at all to these, for example, an antimicrobial -- I keep coming back because I think that's where the real risk is likely to be found, other than sensitization or local tissue damage. Then the corollary of, well, there's not much benefit but not much harm that we know about, on the other hand, the corollary of that would be you should tolerate very little risk. If there's little benefit, one should tolerate very little risk in considering what is approved for use in marketing.

DR. HARRIS: The other comments -- I'd like to just turn back to Question 1, part (e),

and can you read that for us? Oh sorry, actually part (f). Not (e), (f).

DR. DURFOR: Level of evidence: In what situations might pre-clinical in vitro or in vivo animal studies be sufficient to predict the clinical safety and/or effectiveness of a product?

DR. HARRIS: We've touched upon this, but I wanted to give Dr. Elmore any additional opportunity to discuss this as well.

DR. ELMORE: So just to reiterate, I think there -- that we've discussed three situations where animal studies could be beneficial. One would be to prevent contamination of the dressing by external bacteria. The other would be to provide a barrier against microbial entry into a wound. And then the third one would be to extend or to evaluate the number of days that a dressing could be left in place. So I think those are the three that we've come up with.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: We -- excuse me. We also mentioned the potential for maintaining a moist wound environment analysis. And I mean, you could even apply it to the "antimicrobial effect to minimize microbial contamination or colonization."

DR. HARRIS: Dr. Reller.

DR. RELLER: Several times in the discussion, the use of animal models come up. And specific to this question is what role do they play in predicting the clinical safety and effectiveness of the product?

So I have a question for the FDA. It's pretty clearly articulated what the animal rule is in drug, CDER. What is the role of animal rule, or lack thereof, having to do with approval of an indication based on animal data?

I understand, as a prelude to clinical studies, the animal studies may be very useful, but as a basis for approval or a claim, what is the role of animal work in devices?

DR. ASHAR: Hopefully I can answer this, but others from FDA could also provide comment. We do, where we think it is reasonable, use animal studies to help justify claims. You know, as we described for some of these products, or for many of these products, when we think about biocompatibility testing and hindrance of wound healing have been using animal studies.

If this Panel has advice on how we should change the thinking and recalibrate, like I was saying before, to assess these things and other things as we evaluate these products, we would appreciate your recommendations.

I think your question probably also extends to kind of what FDA's authorities are with respect to animal testing and animal review, and I can't personally comment on that. However, I'm not sure the extent to which that's relevant to the discussion that we have at hand here. Hopefully I got at your question, but if not, perhaps others can provide comment from FDA.

DR. CALIFF: Just a point of clarification. When you use the term "animal rule," it has a special significance that I think you know about. When human studies are not ethical, there's an animal rule that allows the FDA to extrapolate directly from animals to people. It's only supposed to be used in situations like terrorism or emerging infections where no one would agree that a human being should be put into a clinical trial.

But I think you may have been referring to the more general situation in CDER, which is that animal studies are used all the time but not for the decision about approval or indication.

DR. RELLER: That's exactly what I'm getting at because one of the barriers to requiring more evidence for the utility of the second component of a combination product is that it's too difficult to do clinical trials, or it's impractical, or one can raise multiple barriers. And so is it conceivable that one would get a claim that has clinical implications

based on the animal testing alone? That's what I'm trying to dissect out.

I understand about it's unethical and -- I mean, with the anthrax, all of that -- but this is, it seems to me, it's how much are we going to depend or will you depend upon the animal data if people conclude that that's the only practical thing to do? And I have some reservations about that.

DR. ASHAR: Well, I think that if the animal model provides a better, more controlled setting for us to evaluate a product, and we think that that information from the animal model is easily translatable to a human clinical setting, then certainly we will use it. But if there's considerations that we need to take into account that would cause us some limitations to the animal model that we need to address in further human clinical studies, whether there be larger studies or just confirmatory studies, you can also provide comment along those lines.

One thing, as a kind of a separate note, I want to make clear to the Panel, and this was brought up by Ms. Lott before, you know, we're looking at these products as a whole, as a device, that of a wound dressing with a drug product together, so separating them out as individual components may be problematic for us to do. Certainly there's many of these chemicals that are OTC monograph drugs; however, they're not necessarily used according to the OTC monograph.

So to take some of the claims from those OTC monograph drugs and simply translate them to our devices is problematic because the OTC monograph drugs need to be used according to their monograph, in which case when you apply them to a dressing, they no longer are necessarily being used in that capacity. So hopefully that clarifies.

DR. ALAM: If I could make one more comment pertaining to the question we were discussing, item (f). Another thing where in vitro or in vivo animal studies may be sufficient, another claim would be "a non-adherent layer reduces pain during dressing changes,"

where the implication seems to be that the non-adherence of the layer is all that's significant. And presumably that could be shown without requiring any kind of living being, even an animal, though I do think it's kind of a bad claim, since it's focusing only on one cause of pain reduction.

DR. HARRIS: If we could take a look now at Question 1e.

DR. DURFOR: Can you help me with these slides? Thank you very much.

Please advise FDA on the additional factors to consider when products contain more than one antimicrobial.

DR. HARRIS: Any comments here?

Dr. Sood.

DR. SOOD: Just a quick comment, that you would want to know if that combination is antagonistic, which is rare, or synergistic or just a combination. So I think that having to take into account how the individual antibiotics react with each other would be an important consideration.

DR. HARRIS: Dr. Reller, I know you have a comment.

DR. RELLER: Only that if it's difficult to assess the addition of one to the intrinsic efficacy of saline, I would make it even more difficult to assess two. And I think the point made about the interaction between the compounds is an important one.

DR. HARRIS: Any thoughts regarding whether that would impact the likelihood of developing resistance?

DR. SOOD: I will start, and hopefully the microbiologists will add to this. But in some cases, I think it could potentially decrease the amount of resistance. If you use a cell wall active agent with a protein synthesis inhibitor, I think you're going to get greater efficacy, and therefore, along the same lines of inhibiting growth completely, that's going to be much less likely to cause resistance.

However, as Dr. Reller pointed out, this is an area of unknown. We don't know exactly what the pharmacokinetics are at the wound, what the pharmacokinetics are in the dressing. So it is a rather complex question to be able to answer easily.

DR. HARRIS: Dr. Patel.

DR. PATEL: So I do think that using more than one antimicrobial agent does pose potentially an increased risk of selecting for resistance. It would definitely be something that would need to be evaluated.

DR. HARRIS: How would you evaluate that is the question.

DR. CALIFF: Sorry. How would you evaluate it?

DR. PATEL: So I think the risk of increasing resistance would be the result of co-selecting a resistance mechanism, one drug selecting for resistance to the other drug. And, you know, specifically, I think that could be assessed by doing studies to select for de novo resistance using the combination and asking whether that selects for new resistance in the bacteria. And then it could also be assessed by testing the combination against a panel of relevant clinical isolates.

DR. ALAM: It's Murad Alam. Can I ask a question? I am very confused now. Is there like a consensus among our microbiology and infectious disease people as to whether this is worse or better? Or is this truly an area where we don't know?

DR. PATEL: It depends upon the combination. So we may know for some combinations, based upon surveillance data, that the risk for selecting for resistance is higher. For other combinations, if we don't have sufficient surveillance data, then it would be a we don't know but should find out.

DR. WOLF: I think with any of these things, you got to be careful that whenever you put things together, oftentimes there's unintended consequences. And we don't know what those consequences are going to be, so that's why you do the experiment. Right?

And you can't go in with preconceived biases about what you're going to see, either.

And so it may be that adding another antimicrobial may, in fact, induce further resistance, or the other way. We don't know. And so I think you have to, if you're going to put two things together, even though both of them don't have any effects, you know, have these known effects by themselves, when you put them together, you may have different things. You just don't know. You have to do the experiment.

DR. SOOD: Hopefully this may be a little bit clarifying, but may be more confusing. I'm not sure. But I think it's two different principles. One is if you're exposed to more antibiotics, you're more likely to become resistant to those antibiotics. And the other principle is if you have multiple drugs, multiple antibiotics attacking a particular organism, you're more likely to suppress it, i.e., hepatitis C, mycobacterial infections, etc.

And then added to that is the levels of all of those medications, because if you're completely suppressing growth, you're not going to have resistance. But if you're just suppressing it enough to have a little bit of growth, then you've now exposed this bacteria to two different antibiotics. So all of those principles have to be weighed in a study to be able to see which of those will be more relevant in the wound dressing itself.

DR. WOLF: And we don't know what those coefficients are going to be until you do the experiment.

MR. KITCHEL: Thank you. Brandon Kitchel. I absolutely agree with that point, and you kind of made most of what I wanted to say.

If I could just make one more distinction between antibiotics and antimicrobials, a lot of times, combination therapies are utilized to have kind of a one-two punch in which you're using two different mechanisms to attack bacteria in a targeted way, specifically with antibiotics. And just to remind the Panel that the antimicrobials in these wound dressings are broad spectrum that contain multiple mechanisms of action within just the one. So I

just wanted to make that point. Thank you.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Along those lines -- and I meant to try and get at this earlier -- I think we've got a vernacular problem. Dr. Gottrup was talking about, in Denmark, how they've seen a decrease in antibiotic resistance. And I'm using antibiotic in the strict sense of the term because the government's controlling it. But everything that we use in the burn world on a daily basis, in Denmark, they consider to be an antiseptic.

Just looking at the FDA definitions, we've got antibacterial, antibiotic, antimicrobial, antiseptic, antiseptic drug, and drug. And, you know, in fact, if you read the definition of a drug here, that covers every single thing that I use on a daily basis medically, frankly, because it doesn't call out specifically that the mechanism of action in this definition has to be chemical. You have to get to that through backing out the definition of a device and backing out the definition of a biologic.

So we need clearer definitions as to what we're dealing with because I mean even Dr. Kitchel just used "antibiotic" and "antimicrobial," same sentence. Is silver in a dressing, is bismuth in xeroform gauze, are those antibiotics or are they antiseptics? Because the definition of antimicrobial involves antibiotics, antivirals, antifungals, and antiseptics.

DR. HARRIS: Dr. Kitchel wants to respond to that.

MR. KITCHEL: Very quickly, yes. And I agree, the terminology has not been consistently used throughout history, so it's kind of a difficult task. But for the purposes of today in this meeting, it's easy to subcategorize the broader term "antimicrobial" as this umbrella term. And we can subcategorize it based off of either the microorganisms that we're trying to treat, so you can have antibacterials, antifungals, anti-algae, antiviral, even though not technically a microorganism, but you get the point of that subcategorization.

The one that we've been using mostly today is for the intended use of that

antimicrobial. So antibiotics and their synthetic counterparts are generally accepted to be, you know, used for the intention of treating a bacterial infection. Antiseptics are accepted for their general use of killing organisms on a living surface or mucoidal membrane. And disinfectants are used for killing bacteria on an inanimate object. So hopefully that helps.

DR. HOLMES: It doesn't. Disinfectant's not even on this list. Let me read you what antimicrobial is defined as for the purpose of this meeting. Quote, "A term to broadly capture antibacterials, antifungals, and antiseptics." End quote. So, I mean, I would put forth we need to come to a consensus as to what do we decide the constituents of these dressings are.

DR. ALAM: Yeah, I think your nosology was very helpful, but if you could just go on and specifically state which terms apply to what we're discussing today, that would be most helpful.

MR. KITCHEL: Happy to do that. So as far as the purpose of including them in the dressings, which is why we're here today, we're kind of in a new territory. It's not technically an antiseptic; it's not technically a disinfectant. We know it's not an antibiotic or a synthetic counterpart of an antibiotic, meaning the purpose is not to treat the organisms in a wound. So that's part of the difficulty in using previously established terminology to talk about where we are today.

DR. CHANG: Cynthia Chang. I'd like to add to this interesting conversation. As you've noticed, there is a lot of confusion and perhaps overlap in the terms that are being used, and that's part of the reason that we're here today. I think, if we try to parse out, you know, the differences between what's an antimicrobial, antibacterial, antibiotic, antiseptic, and what's a drug or device, we may be going somewhere that is not really the purpose of this discussion, which is really to talk about the risks and clinical benefits of the devices and how they're used.

And so I think, without getting into more of the details of how these products are considered in terms of regulatory considerations, we'd really like to focus on the clinical benefits and clinical risks of the products.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: But you're asking us to consider the fate of some 500 to 700 products approved through the 510(k) pathway. I think parsing and getting down to the regulatory nuts and bolts as to how they are classified is hugely material.

DR. HARRIS: Just a point of clarification. I think that the deliberations of our Panel will assist in the process --

DR. HOLMES: Right.

DR. HARRIS: -- but it will not be singularly our decision.

DR. HOLMES: No. No, I understand that. But they brought us here for a reason. And it was a reason that wasn't solved 11 years ago.

(Laughter.)

DR. MILLER: Help me out to understand how much of a problem resistance, emerging resistance to these materials really are. I mean, theoretically, I hear all the discussion, but these have been used for decades, and some for centuries, and I'm not aware that there is a, you know, resistance problem to silver, to chlorine, and these things. I mean, is that a real problem, or is it just theory?

DR. ASHAR: This is Binita Ashar. What we encounter are products that have multiple chemicals in them. Some of them may be known antimicrobials; others purport to have antimicrobial activity. Many times they're used together. And that is the question that we want this Panel to help us with.

In that category of antimicrobial, however you stratify it, you know, there are some things that are botanicals, there are some things that are metal ions, there are some things

that antiseptics, there's some things that are analogous to OTC monograph drugs. And when they're used together, there could be a list of them in any one product. And what is a rational way for us to consider benefit and risk when we're evaluating these devices for some of the claims that we've discussed in Question 5?

DR. PATEL: Yeah. Jean Patel. So I think we have varying levels of data. But I also think that the antimicrobial agents highlighted in our briefing materials as being of particular concern for antimicrobial resistance is the right list. Some examples of concerning resistance are to polymyxin B. We now have plasmid-mediated resistance to polymyxin B. That is turning out to be found in bacteria that also contain carbapenemases, so gram-negative bacteria that would have a carbapenemase that confers resistance to all beta-lactams, MCR-1 that confers resistance to colistin.

These also contain 16S methylases that confer resistance to all the aminoglycosides. Those bacteria have now been reported in five different parts of the world. So that's a gram-negative bacteria that's resistant to all drugs except for tigecycline. So that's an example of a bacteria carrying multiple resistance mechanisms.

Another concern we have with the drugs listed here are chlorhexidine. That is an antimicrobial that's being used widely as a wash to prevent healthcare-associated infections. And the rates of chlorhexidine resistance, they are occurring, but they are low. What's concerning is that it's genetically linked to other types of resistance so that use of chlorhexidine can actually increase rates of resistance to other important antimicrobial agents. So these are examples of the resistance problems we worry about.

DR. HARRIS: You had a question? Dr. Alam, then Dr. Wolf.

DR. ALAM: Hi, it's Murad Alam. I just had a question for FDA. I know there's a concern about resistant organisms and the uncertain risk of resistance. And the other worry I heard was about a possible uptick in adverse event reports of all types coming to

FDA, although we're not sure if those are proportionately higher, given the increase in base rate. But even so, is there any other specific concern FDA has, or any other data FDA has about bad things that are happening with this class of products with no name?

DR. ASHAR: I think you just about covered it. I think, you know, this is a burgeoning portfolio. We have many more products than we did back in 2005. That's reflected by the 700 products, as well as the increase in adverse event reporting, although we don't know whether the adverse events reporting is due to actual increase in adverse events or increase in reporting.

I can't think of -- and then the environment has changed. We know more now than we did back in 2005, so that basically summarizes our concerns.

DR. HARRIS: Quickly.

DR. WOLF: So a couple of things: So as far as it containing products, to answer Dr. Ashar's question, each have to be considered independently. That's what I would say. That's my advice is that, you know, each have to be considered independently and with equipoir [sic]. Right?

DR. ASHAR: So we have one product that would have many of these chemicals within it. So how would one -- walk me through, walk us through how you would consider it.

DR. WOLF: So that particular product, having 500 antibiotics in it, or whatever it is, right, by itself, it is an independent product, and it has to go through all the testing that all the rest of them did, right? Just by adding on stuff, say, well, we did that before with this, well, but does that affect all these other things? We don't know. And so as far as resistance and things like that, it has to be tested and considered independently from all the other dressings that are out there. So that's one thing.

The second question I have, or second issue I have, is in particular for silver, does

anyone in this room know of a single clinical isolate that has ever been isolated that is resistant to silver that caused any attributable morbidity to a patient?

MS. LOTT: Who is testing for that?

DR. WOLF: I don't know but -- so but nobody's done -- so but my question is this is an imagined threat for that, or that thing. And it's possible, it's very possible that that organism could exist, but we haven't seen it. And so should we be taking away potential benefit for these particular -- let's say we take the silver products, just as an example, and made them Class III. Then I can't use that anymore for my patients who have all received benefit from it. I'm just making that a point.

But it's scary if that organism did exist, right? And so there has to be some kind of a way to consider that that could happen, but we shouldn't harm patients right now for a imagined threat.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: That goes back to the point that I was trying to make earlier is that if we are looking at looking at Class II versus Class III devices, in order to make strong comparative analysis, we need robust datasets that we could possibly get through Class III regulation. If we have a Class II regulation, on the other hand, now we have products that can slip by based on empiric evidence previously, much like what happened with another device that I evaluated on a previous panel. And so that is very concerning to me.

DR. HARRIS: Quickly. Dr. Sood.

DR. SOOD: Sorry. I just wanted to add that we may not know of isolates that are silver-resistant, but things like povidone-iodine, we have seen *Pseudomonas* and other types of outbreaks associated with resistance to those antiseptics. So I suspect that there is a similar situation with silver, and we may not know it as readily.

DR. HARRIS: Before we wrap things up, could we please take a quick look at

Question 3.

DR. DURFOR: The benefit/risk, individual and societal: Please comment on the following questions in the context of infected and non-infected acute, chronic, and burn wounds (excluding burns that require skin grafts):

Is reduction of colony count on the dressing predictive of clinical benefit to the patient? If yes:

a. What is this clinical benefit?

b. What is the evidentiary basis?

c. And how does one balance this with the risks to patient and society?

DR. HARRIS: Comments, anyone? So do we think it's important to have a reduced -- I don't know who's actually measuring colony counts on dressings.

DR. CALIFF: Oh, I mean, it came to my attention, as I was preparing for this with colleagues, that it's a claim that's made, reduced bioburden. In fact, we heard it today. And it seems like a pretty straightforward empirical question that could be answered relatively easily by a research network in a consortium with industry, for example, if it hasn't. But if we know the answer, that's why we're asking the question.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: From an empiric standpoint in burns -- some of these guys aren't old enough to go back and realize what it was like back in the '60s. I had a burn in the '60s that was greater than 20% that I was fortunate enough to not have any of the available agents we have now, including Silvadene, which is a drug.

That having been said, with the patients that we treat nowadays, we feel like that what we're doing -- and correct me if I'm wrong -- with the addition of this type of dressing, as well as some of the changes we've made with the earlier excisions and things like that, that we have made a huge difference because our mortality rate has plummeted.

Now, you take that into consideration and say, well, let's do a controlled study and put the dressing on and not any of the things that are in the dressing, such as the silver. Count me out because I don't want to run that risk because I don't think that is an ethical study that I could take a part in.

So I think that we do have evidence, although based upon observational status of what we do, that it has been beneficial.

DR. HARRIS: Dr. Miller.

DR. MILLER: I think that you were discussing burn wounds, but I think for other kinds of wounds, I'm not convinced that there is any clinical benefit to having a dressing with antibiotics in it, except to keep the colony count down in the dressing so that you don't smell it. And I mean, in terms of contaminating the wound, if you put a clean dressing on somebody, and there is enough exudate, then there is -- if you clean the wound up surgically and you dress it, then you're going to have exudate. But if it's dressed properly, the colony count will stay low in the dressing, unless the wound itself is the source of the bacteria.

You know, if the wound itself is a source of bacteria, then the dressing will not treat that, you know, so I'm unconvinced of the clinical benefit.

And just one more comment, if I may. I mean, I'm not sure -- you know, I think the thing we have to decide is are these things of value for wound healing and lowering infection rates? If they're not, then I'm not sure we should put, you know, people through a lot of expensive studies to prove that colony counts go down on the dressing, because what difference does it make? You know, I mean, we're going to force them to do it, but okay, now we know exhaustively, exactly what happens in the dressing, but it doesn't make any difference anyway. So why force that to happen unless we know it's important? So --

DR. HARRIS: Dr. Wolf.

DR. WOLF: I'll give an example from the literature. There is a dressing called Biobrane. I'm sure you're familiar with it. If you put that on patients -- it has no antimicrobial in it. If you put that on a partial thickness wound, almost always it adheres, and then the wound heals underneath it, and it comes off, except when it doesn't. Right?

And there was a study out of Australia, what, 2, 3 years ago now, something like that, where they showed the difference between children and adults. Adults are more prone to infection with the use of Biobrane, and it was like I want to say 5, 10%, something like that. So, you know, most people are going to be fine without it. But that's without an anti -- that's out without an antimicrobial in it, and guess what, they got an infection.

And so I think you're right in that almost always, there's no -- that including an antimicrobial doesn't mean much if the wound is clean. When you put Biobrane on, supposedly the wound is clean, but occasionally you're going to get it. And then if you had treated that with, I don't know, something that has an antimicrobial in it, would the same thing have happened? We don't know. You got to do the experiment.

DR. HARRIS: Okay. Oh. Dr. Ashar.

DR. ASHAR: Sorry. I just wanted to add, you know, while we're focusing on benefits in this discussion, and we've talked about some of the risks, with respect to antimicrobial resistance, please also consider other risks, for example, possible absorption of the product within the wound or the local toxicity. We've touched on some of those things, but just to bring that to the attention of the Panel.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Dr. Harris, one other thing, that even with that clean wound, though, that if we were to look at Dr. Schultz's presentation from earlier today, that said we got rid of the biofilm, and if you left it alone, within 48 to 72 hours, it was back. On the other hand, if it had an antimicrobial barrier on top, that may not be the case.

DR. HARRIS: Okay. So at this time, the Panel is prepared to hear summations, comments, and clarifications from FDA.

DR. ASHAR: I have no comments.

DR. HARRIS: Okay. Commissioner?

DR. CALIFF: Having a bully pulpit, I feel compelled to give a comment, whether for better or worse. First of all, I just want to reassure people -- well, first, let me say it's a privilege to be part of a panel. It does make me feel good, like going back to the good old days. And it's an amazing thing when smart people with clinical and empirical experience and knowledge come together over a difficult problem, to hear the different perspectives and see where there's agreement and disagreement. I think this Panel has achieved that.

But for those who are worried, I just want to reassure everybody, it's a principle at FDA that the Commissioner, as a political appointee, does not delve into the decisions that are made by individual centers about their activities. So I participate in the Panel, but the follow-up and tomorrow's activities will be activities of the relevant centers and other people. And, you know, I've expressed some opinions and ideas here, but I wanted to be clear that it's not my job to make these decisions. Others will do that. But thanks again for including me.

And, you know, I do also just finally add that I think we realize that we presented a very difficult dilemma with regard to antimicrobial resistance, but much like the opioid crisis that we have, where societal considerations begin to play in, in a way that you wouldn't consider other therapeutics, there's an issue here. And we haven't helped you much because we're learning at the same time that you are.

So we're mostly interested in your opinions, given the uncertainty of how you would weigh the societal risk, the risk to the individual and the benefits to the individual, as you look at these products.

DR. HARRIS: Any last minute comments? Well, if not, thank you very much for your participation today, and we will resume our discussion tomorrow morning at 8 o'clock. Thank you.

(Whereupon, at 4:54 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

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Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY J. ATKINSON, JR.

Official Reporter